CHRONIC TOXICITY SUMMARY

1,4-DICHLOROBENZENE

(p-dichlorobenzene; di-chloricide; p-dichlorobenzol; Paradow; Paramoth; Parazene; p-chlorophenyl chloride)

CAS Registry Number: 106-46-7

I. Chronic Toxicity Summary

Inhalation reference exposure level	**800 µg/m^3** (U.S. EPA-RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC.
Critical effect(s)	General effects (reduced body weights and food consumption) in rats CNS effects (tremors) in rats Respiratory/dermal effects (nasal and ocular discharge) in rats Liver effects (increased liver weight) in rats, and Kidney effects (increased kidney weight) in rats.
Hazard index target(s)	Nervous system; respiratory system; alimentary system; kidney

II. Chemical Property Summary (HSDB, 1997)

Description	White crystals, monoclinic prisms
Molecular formula	$C_6H_4Cl_2$
Molecular weight	147.01
Boiling point	174°C
Melting point	53.1°C (sublimes)
Vapor pressure	10 mm Hg atm @ 54.8 °C
Solubility	Soluble in chloroform, carbon disulfide, alcohol, ether, acetone, benzene
Conversion factor	1 ppm = 6.0 mg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Commercial grade 1,4-dichlorobenzene (1,4-DCB) is available in the USA as a technical grade liquid, typically containing a small percentage (>0.1% by weight) of meta and ortho isomers; as a solution in solvent or oil suspension; or as crystalline material pressed into various forms (HSDB, 1997). Besides its role as an intermediate in the synthesis of various organics, dyes and pharmaceuticals, 1,4-dichlorobenzene is used as a space or garbage deodorizer for odor control. The insecticidal and germicidal properties of 1,4-

dichlorobenzene are used to control fruit borers and ants, moths, blue mold in tobacco seed beds, and mildew and mold on leather or fabrics.

IV. Effects of Human Exposure

Case reports of human exposure to 1,4-DCB include malaise, nausea, hepatic manifestations (yellow atrophy and cirrhosis), proteinuria, bilirubinuria, hematuria, and anemia. A woman exposed to 1,4-DCB for 6 years developed central nervous system effects, including severe cerebellar ataxia, dysarthria, weakness in all limbs, and hyporeflexia (U.S. EPA, 1985).

No epidemiologic studies of 1,4-DCB exposures were located.

V. Effects of Animal Exposure

CNS effects have been observed in rats, rabbits and guinea pigs exposed to 0, 96, 158, 341 or 798 ppm (0, 577, 950, 2050 or 4800 mg/m^3) 1,4-DCB by inhalation 7 hours/day, 5 days/week for 6-7 months (Hollingsworth *et al.*, 1956). High dose animals showed marked tremors, weakness, loss of weight, eye irritation and unconsciousness. Liver and kidney changes included cloudy swelling and centrilobular cellular degeneration (liver). In another inhalation study in rats animals were exposed to 0, 75 or 500 ppm (0, 451 or 3006 mg/m^3) for 5 hours/day, 5 days/week for 76 weeks (Riley *et al.*, 1980). The authors found increased kidney and liver weights in the high dose group: a 16% increase at 26 weeks, 33% at 76 weeks, and 10% at 32 weeks post-exposure. Studies with oral exposure to 1,4-DCB, including the NTP (1987) chronic bioassay study (maximum dose of 300 mg/kg-day), have also found an increased incidence of renal and hepatic lesions (cellular degeneration and focal necrosis).

Three inhalation reproductive studies, one in rabbits (Hayes *et al.*, 1985), one in mice (Anderson and Hodge, 1976), and one in rats (Chlorobenzene Producers Assn., 1986), found minimal reproductive effects. In rabbits exposed on days 6-18 of gestation to 100, 300, and 800 ppm 1,4-DCB, only the differences in percentage of implantations reabsorbed and in percentage of litters with resorptions group were significantly increased and only in the 300 ppm group (Hayes *et al.*, 1985). No reduction in reproductive performance was observed in mice exposed to 0, 75, 225, or 450 ppm 1,4-DCB for 6 hours/day for 5 days (Anderson and Hodge, 1976).

In a two-generation reproductive study, Sprague-Dawley rats P1 (28/sex/group) were exposed to 0, 50, 150 or 450 ppm (0, 301, 902, or 2705 mg/m^3) of 1,4-DCB vapor for 10 weeks, 6 hours/day, 7 days/week, then mated for 3 weeks. The second generation F1 weanlings were exposed to 1,4-DCB for 11 weeks then mated. No developmental abnormalities were observed in pups examined. At 450 ppm a significant decrease in live births, pup weights, and pup survival were seen in both the F1 and F2 generations. Non-reproductive effects observed in the parental males in the 150 and 450 ppm groups included significantly increased liver and kidney weights (Chlorobenzene Producers Association, 1986). All dose levels caused hyaline droplet nephrosis in post-pubescent males; but this change was

associated with the formation of alpha-2u-globulin, an abnormality considered specific for male rats with no relative human significance (U.S. EPA, 1991). The Chlorobenzene Producers Association reproductive study was chosen by the U.S. EPA to derive the RfC.

VI. Derivation of U.S. EPA Reference Concentration (RfC)

Study	Chlorobenzene Producers Association, 1986 (evaluated by U.S. EPA, 1994)
Study population	Sprague-Dawley rats (28 rats/sex/group)
Exposure method	Discontinuous whole-body inhalation exposures (0, 50, 150 or 450 ppm) over 10 weeks
Critical effects	Reduced body weights and food consumption; tremors; nasal and ocular discharge; increased liver and kidney weights
LOAEL	150 ppm
NOAEL	50 ppm
Exposure continuity	6 hr/day for 7 days/week
Average experimental exposure	13 ppm for NOAEL group
Human equivalent concentration	13 ppm for NOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
Exposure duration	10 weeks
LOAEL uncertainty factor	1
Subchronic uncertainty factor	3
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	0.1 ppm (100 ppb, 0.8 mg/m^3, 800 µg/m^3)

A 3-fold subchronic uncertainty factor was used because of data suggesting limited progression of hepatic lesions (Riley *et al.*, 1980).

The major strengths of the REL are the observation of a NOAEL and the demonstration of a dose-response relationship. The major uncertainties are the lack of human data and the lack of chronic, multiple-species health effects data.

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CHRONIC TOXICITY SUMMARY

1,1-DICHLOROETHYLENE

(DCE; 1,1-dichloroethene; VDC; vinylidene chloride)

CAS Registry Number: 73-35-4

I. Chronic Toxicity Summary

Inhalation reference exposure level	**20 μg/m^3**
Critical effect(s)	Increased mortality; hepatic effects (mottled livers and increases in liver enzymes) in guinea pigs
Hazard index target(s)	Alimentary system

II. Physical and Chemical Properties (HSDB, 1994)

Description	Colorless liquid
Molecular formula	$C_2H_2Cl_2$
Molecular weight	96.95
Boiling point	31.7°C
Vapor pressure	500 mm Hg @ 20°C
Solubility	Soluble in water (2.5 g/L); miscible in organic solvents
Conversion factor	3.97 μg/m^3 per ppb at 25 °C

III. Major Uses and Sources

1,1-Dichloroethylene (1,1-DCE) is used in the production of polyvinylidene chloride copolymers (HSDB, 1994). 1,1-DCE containing copolymers include other compounds such as acrylonitrile, vinyl chloride, methacrylonitrile, and methacrylate. These copolymers are used in flexible packaging materials; as flame retardant coatings for fiber, carpet backing, and piping; as coating for steel pipes; and in adhesive applications. Flexible films for food packaging, such as SARAN and VELON wraps, use such polyvinylidene chloride copolymers.

IV. Effects of Human Exposure

Limited information exists regarding the human health effects following exposure to 1,1-DCE. A few case reports and mortality studies have reported hepatotoxicity and nephrotoxicity after repeated, low-level exposures (USEPA, 1976; Ott *et al.*, 1976). However, these investigations were conducted in industrial settings with the possibility of

mixed chemical exposures. In preliminary clinical findings reported by the EPA (1976), workers exposed to 1,1-DCE for 6 years or less had a high incidence of hepatotoxicity, with liver scans and measurements of liver enzymes revealing 50% or greater loss in liver function in 27 of 46 exposed workers. Unfortunately, no follow-up study was reported.

V. Effects of Animal Exposure

Several studies have reported on the subchronic or chronic toxicity of 1,1-DCE in laboratory animals exposed either via oral or inhalation routes. The liver is the primary target organ of 1,1-DCE toxicity following acute or chronic inhalation exposure. Such exposure is marked by both biochemical changes (alterations in serum enzyme levels) and histological changes (e.g., midzonal and centrilobular swelling, degeneration, and necrosis) (Gage, 1970; Lee *et al.*, 1977; Plummer *et al.*, 1990; Quast, 1976; Quast *et al.*, 1986). Unfortunately, these longer-term studies used only one or two doses or a limited number of animals.

Male and female rats exposed intermittently (6 hours/day, 5 days/week) to 125 or 200 ppm 1,1-DCE over 30 days exhibited centrilobular fatty degeneration or hepatocellular necrosis (Quast 1976, as cited by USDHHS, 1994). Two other studies identified hepatic changes in rats at lower concentrations of 1,1-DCE (6 hours/day, 5 days/week): cytoplasmic vacuolation after 30- or 90-day exposure to 25 or 75 ppm 1,1-DCE (Balmer *et al.*, 1976, as cited by USDHHS, 1994), and fatty changes after 6 months at 25 ppm 1,1-DCE (Quast *et al.*, 1986).

Laboratory animals appear less tolerant of continuous exposure (23-24 hours per day) than intermittent exposure. Beagle dogs exposed to 100 ppm 1,1-DCE for 8 hours/day, 5 days/week for 42 days had no evidence of hepatotoxicity, but continuous exposure to 48 ppm for 90 days caused liver changes (Prendergast *et al.*, 1967). Similarly, monkeys continuously exposed to 48 ppm for 90 days exhibited focal necrosis and hemosiderin deposition, while no liver toxicity was apparent following 42 days of intermittent exposure to 100 ppm 1,1-DCE (Prendergast *et al.*, 1967). Guinea pigs exposed to 1,1-DCE for 24 hours per day for 90 days (0, 5, 15, 25, or 48 ppm) displayed mottled livers at 15 ppm, and increased liver enzyme levels (SGPT and AP) at 48 ppm. A NOAEL of 5 ppm based on liver changes (Prendergast *et al.*, 1967) is indicated by the results.

Additional adverse effects observed to a lesser extent in laboratory animals include respiratory and renal toxicity. Nephrotoxicity observed following chronic 1,1-DCE exposure included gross organ (increases in kidney weight) (Klimisch *et al.*, 1979; Quast *et al.*, 1986) and histological changes (tubular swelling, degeneration, and necrosis) (Klimisch *et al.*, 1979; Lee *et al.*, 1977; Prendergast *et al.*, 1967). Continuous exposure of rats to 48 ppm 1,1-DCE for 90 days caused nuclear hypertrophy of the renal tubular epithelium (Prendergast *et al.*, 1976). Mice exposed to 25 ppm 1,1-DCE 4 hours/day, 4 or 5 days/week, for 52 weeks displayed severe tubular nephrotoxicity (Maltoni *et al.*, 1985 as cited by USDHHS, 1994). Nasal irritation was observed in rats exposed to 200 ppm for 4 weeks (Gage 1970). But no respiratory effects were attributed to 1,1-DCE exposure in rats, monkeys, dogs, rabbits, or guinea pigs exposed to 100 ppm intermittently for 6 weeks (Prendergast *et al.*, 1967) or in rats exposed to 75 ppm for 18 months (Quast *et al.*, 1986).

Toxicokinetic studies in laboratory animals have demonstrated that 1,1-DCE is readily absorbed and rapidly distributed following inhalation exposure (Dallas *et al.*, 1983; McKenna *et al.*, 1978b). Following inhalation exposure to radioactively labeled 1,1-DCE, rats preferentially accumulate radioactivity in the kidney and liver (McKenna *et al.*, 1978b; Jaeger *et al.*, 1977). Glutathione (GSH) conjugation appears to be the major detoxification route for 1,1-DCE intermediates, and GSH-depleting experimental states, such as drugs and fasting, may tend to increase 1,1-DCE toxicity (Jaeger *et al.*, 1977; McKenna *et al.*, 1978; Reichert *et al.*, 1978). One study greatly increased 1,1-DCE induced lethality and hepatotoxicity in rats by pretreatment with acetaminophen (Wright and Moore, 1991).

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Prendergast *et al.* (1967)
Study population	Guinea pigs (15 per group, except 45 animals in 20 mg/m^3 group)
Exposure method	Continuous whole body inhalation (0, 20, 61, 101, or 189 mg/m^3)
Critical effects	Increased mortality at 61, 101, to 189 mg/m^3; hepatic effects (mottled livers and increases in SGPT and AP enzymes) noted at 189 mg/m^3
LOAEL	61 mg/m^3
NOAEL	20 mg/m^3
Exposure continuity	Continuous
Exposure duration	90 days
Average experimental exposure	20 mg/m^3 for NOAEL group
LOAEL factor	1
Subchronic uncertainty factor	10 (since guinea pig life-span is about 6 years)
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	1000
Inhalation reference exposure level	0.02 mg/m^3 (20 $\mu g/m^3$; 0.005 ppm; 5 ppb)

The principal study (Prendergast *et al.*, 1967) identified adverse hepatic and/or renal effects in rats (15 or 45/group), guinea pigs (15 or 45/group), dogs (2 or 6/group), and monkeys (3, 9, or 21/group) exposed to inhaled 1,1-DCE. Continuous exposure to 1,1-DCE, 24 hours/day over 90 days, demonstrated more severe effects than intermittent exposure, 6 hours/day, 5 days/week for 6 weeks, in the species tested. Unlike the other available subchronic and chronic studies, this principal study included multiple exposure levels of 0, 5, 15, 25 and 48 ppm (0, 20, 61, 101, and 189 mg/m^3). Mortality, hematologic and body weight data were well tabulated and presented in this study. Histopathologic evaluation was conducted on the heart, lung, liver, spleen and kidneys. Following continuous exposure, adverse hepatic effects included focal necrosis in monkeys (LOAEL 189 mg/m^3, NOAEL 101 mg/m^3), in dogs (LOAEL 189 mg/m^3, NOAEL 101 mg/m^3), in rats (LOAEL 189 mg/m^3, NOAEL 101 mg/m^3); and altered lipid content and increases in SGPT and alkaline phosphatase in guinea

pigs (LOAEL 189, NOAEL 20 mg/m^3). Additionally, renal alterations were observed in rats as nuclear hypertrophy in the tubular epithelium (LOAEL 189 mg/m^3, NOAEL 61 mg/m^3). Monkeys exposed to 1,1-DCE also displayed a greater than 25% decrease in body weight (LOAEL 189 mg/m^3, NOAEL 20 mg/m^3). The subchronic study by Prendergast *et al.* (1967) was chosen over the chronic studies because of its better design, its use of continuous exposure, and its exhibition of toxic effects below the LOAELs reported in the other studies.

Although limited in number, the other chronic and subchronic studies available consistently demonstrate adverse hepatic effects following 1,1-DCE exposure (Lee *et al.*, 1977; Maltoni *et al.*, 1985; Plummer *et al.*, 1990; Quast *et al.*, 1986). Hepatocellular fatty change was observed in rats exposed to 25 ppm or 75 ppm 1,1-DCE intermittently (6 hrs/d, 5 d/wk) for 18 months. This mid-zonal fatty change was also observed at the 12-month interim sacrifice, but did not appear to progress in severity or incidence over time (Quast *et al.*, 1986). A more severe hepatocellular necrosis and renal tubular necrosis were observed in mice exposed to 55 ppm 1,1-DCE 6 hr/d, 5 d/week for 1 year (Lee *et al.*, 1977).

Uncertainty factors are appropriate due to the limited number of subchronic and chronic inhalation studies (greater 1 year duration) in laboratory animals. In addition, few industrial surveys and epidemiological studies are available on the adverse effects of 1,1-DCE in humans; these are limited by small sample size, short follow-up, and/or brief exposure periods. But this limited evidence does suggest an association between repeated exposure to 1,1-DCE and liver damage in humans (EPA, 1976). No toxicokinetic data regarding the absorption, distribution, metabolism or excretion of 1,1-DCE in humans is available.

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CHRONIC TOXICITY SUMMARY

DIETHANOLAMINE

(DEA; 2,2'-iminodiethanol; 2,2'-iminobisethanol; diethylolamine; 2,2'-aminodiethanol; 2,2'-dihydroxydiethylamine)

CAS Registry Number: 111-42-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**20 μg/m^3**
Oral reference exposure level	**0.005 mg/kg-day**
Critical effect(s)	Microcytic anemia, decreased corpuscular hemoglobin and corpuscular volume in rats
Hazard index target(s)	Cardiovascular system; nervous system

II. Physical and Chemical Properties (Melnick and Thomaszewski, 1990; Dow, 1980)

Description	Colorless crystals
Molecular formula	$C_4H_{11}NO_2$
Molecular weight	105.14
Density	1.097 g/cm^3 @ 20°C
Boiling point	268.8°C @ 760 mm Hg
Vapor pressure	0.00014 mm Hg @ 25°C
Solubility	Soluble in alcohol, water, acetone
Conversion factor	1 ppm = 4.3 mg/m^3 @ 25°C

III. Major Uses and Sources

Diethanolamine is used in the formation of soaps, emulsifiers, thickeners, wetting agents, and detergents in cosmetic formulations (Melnick and Thomaszewski, 1990). It is used as a dispersing agent in some agricultural chemicals, as an absorbent for acidic gases, as a humectant, as an intermediate in the synthesis of morpholine, as a corrosion inhibitor, and as a component in textile specialty agents (Beyer *et al.*, 1983). Diethanolamine is permitted in articles intended for use in production, processing, or packaging of food (CFR, 1981; cited in Melnick and Thomaszewski, 1990). It is also found in adhesives, sealants, and cutting fluids (Melnick and Thomaszewski, 1990).

IV. Effects of Chronic Exposures to Humans

There have been no controlled or epidemiological studies of diethanolamine exposure in humans.

V. Effects of Exposures in Animals

Diethanolamine replaces choline in phospholipids (Blum *et al.*, 1972). Systemic toxicity consequently occurs in many tissue types including the nervous system, liver, kidney, and blood system. The direct effects of DEA on the respiratory system are unknown since no subchronic or chronic inhalation studies have been conducted. Effects of DEA on the respiratory system following oral or dermal exposures have also not been examined.

A 13-week drinking water study in rats (10 per sex per group) showed significant dose-dependent hematological changes following exposure to DEA at all concentrations tested: 320, 630, 1250, 2500, and 5000 ppm in males, and 160, 320, 630, 1250, and 2500 ppm in females. Hematological effects included decreased hemoglobin and mean corpuscular volume (Melnick *et al.*, 1994a). Similar hematological changes were observed following daily topical treatment. In addition to the hematological effects, female rats also showed dose-dependent spinal cord and medullary demyelination beginning at a drinking water concentration of 1250 ppm DEA. Male rats displayed demyelination beginning at 2500 ppm. Female rats gained significantly less weight than controls beginning at 63 mg/kg/day topical treatment. In a companion drinking water study (Melnick *et al.*, 1994b), mice (10 per sex per group) were exposed to concentrations of 0, 630, 1250, 2500, 5000, and 10,000 ppm DEA and displayed dose-dependent hepatotoxicity, nephrotoxicity, and cardiac toxicity. Daily topical treatment in a separate study resulted in skin lesions in mice. Significant hepatic toxicity was observed at all drinking water concentrations, and skin lesions were observed at all topical doses.

Barbee and Hartung (1979a) found that repeated treatment of rats with 330 mg DEA/kg/day significantly inhibited formation of phosphatidyl choline and phosphatidyl ethanolamine in the liver as compared with control rats. In a subsequent study, Barbee and Hartung (1979b) noted changes in liver mitochondrial activity in rats (4 per group) following exposure to DEA in drinking water for up to 5 weeks. Mitochondrial changes were observed at 42 mg/kg/day after 2 weeks.

Daily oral treatment of male rats with 0, 250, 500, or 750 mg/kg/day for 5 days, or 100 mg/kg/day for 14 days resulted in reduced activities of the liver enzymes microsomal hydroxylase and N-demethylase activities (Foster *et al.*, 1971).

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Melnick *et al.* (1994a)
Study population	Rats (female)
Exposure method	Drinking water (*ad libitum*)
Critical effects	Hematological changes (decreased total and mean corpuscular hemoglobin, decreased mean corpuscular volume)
LOAEL	160 mg/L (14 mg/kg/day estimated from water consumption data)
NOAEL	Not observed
Exposure duration	13 weeks
Average exposure concentration	14 mg/kg/day for LOAEL group
LOAEL uncertainty factor	10
Subchronic uncertainty factor	3
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	3,000
Oral reference exposure level	0.005 mg/kg-day
Route-to-route conversion factor	3,500 $\mu g/m^3$ per mg/kg-day
Inhalation reference exposure level	20 $\mu g/m^3$ (4 ppb)

No chronic inhalation studies with diethanolamine were located in the peer-reviewed literature. The study by Melnick *et al.* (1994a) shows dose-dependent adverse hematological and CNS effects in rats exposed to DEA in drinking water. Similar systemic effects were observed following dermal exposure. The Melnick *et al.* subchronic study was of the longest duration and was the most comprehensive report of the systemic effects of DEA in the literature. However, portal-of-entry effects of DEA have not been examined and should be addressed in future studies since this compound has irritant properties. The data from female rats were used since females were more sensitive than males to the hematologic effects of DEA.

The diethanolamine database is relatively weak. Major areas of uncertainty are the lack of adequate human exposure data, the absence of a NOAEL in the major study, the lack of reproductive and developmental toxicity studies, and the lack of chronic inhalation, multiple-species, health effects data.

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CHRONIC TOXICITY SUMMARY

N,N-DIMETHYLFORMAMIDE

(N-formyldimethylamine)

CAS Registry Number: 68-12-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**30 µg/m^3** (U.S. EPA-RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC.
Critical effect(s)	Liver dysfunction and respiratory irritation in humans
Hazard index target(s)	Alimentary system, respiratory system

II. Chemical Property Summary (HSDB, 1994)

Description	Colorless to very slightly yellow liquid
Molecular formula	C_3H_7NO
Molecular weight	73.09
Boiling point	153° C
Melting point	-61° C
Vapor pressure	3.7 mm Hg @ 25° C
Solubility	Soluble in alcohol, ether, acetone, benzene, and chloroform; miscible with water
Conversion factor	2.99 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Dimethylformamide (DMF) is primarily used as a solvent in the production of polyurethane products and acrylic fibers. It is also used in the pharmaceutical industry, in the formulation of pesticides, and in the manufacture of synthetic leathers, fibers, films, and surface coatings (Howard, 1993; Gescher, 1993; Redlich *et al.*, 1988). DMF may be emitted to the environment as a result of its use in a variety of petrochemical industries (Howard, 1993).

IV. Effects of Human Exposure

Among 100 workers occupationally exposed to a DMF for at least one year (mean exposure of 5 years), a statistically significant incidence of hepatic impairment, as indicated by elevated gamma-glutamyl transpeptidase levels and digestive disturbances, were noted (Cirla *et al.*, 1984). Other changes that were not statistically significant included increased SGOT and

SGPT and enlarged livers. The mean time-weighted average concentration of DMF was 22 mg/m^3. Symptoms of irritation occurring only during work at statistically significantly higher incidences included watery eyes, dry throat, and coughing. Also, the exposed workers reported a reduced sense of smell and dry coughs at home with a statistically significant difference as compared to controls. Several of the DMF exposed workers also reported alcohol intolerance characterized by a disulfiram-type reaction (facial flushing and palpitations following alcohol ingestion). Alcohol consumption, a potential confounder, was controlled for in the study design.

A similar study was conducted on workers who had been employed in an acrylic acid fiber plant for more than 5 years (Cantenacci *et al.*, 1984). Concentrations to which the workers were exposed were characterized as either an 8-hour TWA of 18 mg/m^3 or an 8-hour TWA of 3 mg/m^3. Measures of liver function including SGOT, SGPT, gamma-glutamyl transferase, and alkaline phosphatase levels were not significantly different between exposed and unexposed workers. However, the U.S. EPA cautions that because only 54 matched pairs of workers were examined, the power of this study was not high enough to reliably detect a difference in enzyme levels.

U.S. EPA (1994) states that subjective evidence of liver toxicity such as digestive impairment and alcohol intolerance, are often observed at exposures below those which cause clinical changes in liver enzymes. Thus, the symptoms may be more sensitive indicators of hepatic impairment.

Three unexplained cases of small-for-date third trimester intrauterine deaths were observed in a group of women working as quality control analysts in the pharmaceutical industry (Farquhason *et al.*, 1983). This represented a 30% stillbirth rate as compared with the average for the general population of about 0.26%. While the authors concluded that the occurrence of stillbirth in these women was not likely due to chance, the effects cannot be solely attributed to DMF because the women were exposed to other agents in addition to DMF.

V. Effects of Animal Exposure

A developmental toxicity study using three species (mice, rabbits and rats) and four routes of administration (oral, inhalation, dermal and intraperitoneal) identified the rabbit as the most sensitive of the three species. Groups of 15 pregnant rabbits were exposed for 6 hours per day on days 8-20 of gestation to 50, 150, or 450 ppm (150, 449, or 1350 mg/m^3) DMF (Hellwig *et al.*, 1991). Slight maternal toxicity, as indicated by non-statistically significant decreases in maternal body weight gain, was observed in the 450 ppm exposure group. An increased number of total malformations per litter was observed in the 450 ppm exposure group. Malformations observed at statistically higher incidences compared to controls included hernia umbilicalis, external variations, pseudoankylosis of the forelimbs, and skeletal variation and retardation. The authors conclude that there was a clear teratogenic effect in rabbits following maternal exposure to 450 ppm DMF and a marginal effect following exposure to 150 ppm DMF. A NOAEL of 50 ppm for fetal and maternal effects was reported.

Inhalation exposure to 150 ppm was calculated by the authors to approximate a daily dose of 45 mg/kg/day, which coincides with previous work on this compound in this species.

VI. Derivation of U.S. EPA Reference Concentration (RfC) (U.S. EPA, 1994)

Study	Cirla *et al.*, 1984; Catenacci *et al.*, 1984
Study population	Occupationally exposed workers
Exposure method	Discontinuous inhalation exposures
Critical effects	Digestive disturbances and slight hepatic changes
LOAEL	22 mg/m^3
NOAEL	Not observed
Exposure continuity	8 hr/day (10 m^3/day), 5 days/week (assumed)
Average occupational exposure	7.9 mg/m^3 for LOAEL group (22 x 10/20 x 5/7)
Human equivalent concentration	7.9 mg/m^3
Exposure duration	5 years (mean exposure duration)
LOAEL uncertainty factor	3
Subchronic uncertainty factor	3
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Modifying factors	3 (lack of reproductive toxicity data)
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.03 mg/m^3 (30 $\mu g/m^3$, 0.009 ppm, 9 ppb)

Intermediate uncertainty factors were used for LOAEL and subchronic extrapolation because of the mild nature of the effects observed and the only slightly less than chronic exposure duration.

The major strength of the RfC is the availability of human health effects data over several years of exposure. The major uncertainties are the difficulty in estimating exposure patterns and magnitude, the lack of a NOAEL observation, and the lack of complete reproductive and developmental toxicity data.

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CHRONIC TOXICITY SUMMARY

EPICHLOROHYDRIN

(1-chloro-2,3-epoxy-propane)

CAS Registry Number: 106-89-8

I. Chronic Toxicity Summary

Inhalation reference exposure level	**1 μg/m^3** (U.S. EPA RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC
Critical effects	Histological changes in nasal turbinates in rats
Hazard index target(s)	Respiratory system; eyes

II. Physical and Chemical Properties (HSDB, 1997)

Description	Colorless liquid
Molecular formula	C_3H_3ClO
Molecular weight	92.5
Density	1.181 g/cm^3 @ 20° C
Boiling point	116.5° C
Vapor pressure	13 mm Hg @ 20° C
Solubility	Slightly soluble in water, soluble in most organic solvents
Conversion factor	1 ppm = 3.78 mg/m^3 @ 25° C

III. Major Uses and Sources

Epichlorohydrin is a major raw material used in the manufacture of epoxy and phenoxy resins. It is also used as a solvent and in the synthesis of glycerol. Other uses include that of insect fumigation and as a chemical intermediate for the formation of glycidyl acrylate derivatives such as those used in the formation of eyeglass lenses (HSDB, 1994).

IV. Effects of Exposures to Humans

Studies of male reproductive function have shown no evidence of decreased sperm counts in populations occupationally exposed to epichlorohydrin (Milby *et al.*, 1981).

V. Effects of Exposures in Animals

Rats were exposed for 136 weeks (6 hours/day, 5 days/week) to 0, 10, 30, or 100 ppm (0, 38, 113, or 380 mg/m^3) epichlorohydrin (Laskin *et al.*, 1980). Kidney damage in the form of renal tubular degeneration and dilatation was observed in rats exposed to 30 ppm or greater. The observation of severe inflammation in the nasal passages of 90% of the control animals, as well as in the treated animals, prevented comparison of this effect between the two groups.

A subchronic exposure of rats to 9, 17, 27, 56, or 120 ppm (34, 64, 102, 212, or 454 mg/m^3) for 6 hours/day, 5 days/week for 11-19 exposures showed evidence of extrarespiratory effects. These included liver congestion and necrosis and tubular atrophy in the kidneys at the highest concentration (Gage, 1959). Lethargy and weight loss were observed at 56 ppm.

A study on the effects of epichlorohydrin exposure for 10 weeks (6 hours/day, 5 days/week) on male and female fertility in rats and rabbits showed that male rats exposed to 50 ppm (189 mg/m^3) were significantly less fertile than controls, as measured by successful matings to unexposed females (John *et al.*, 1979; 1983a). No histological changes were observed in the testes of the male rats at the end of exposure. No significant effects on fertility occurred in the exposed female rats. Degenerative changes in the nasal epithelium were observed in the female rats exposed to 25 ppm (94.5 mg/m^3), and in both sexes at 50 ppm.

A teratology study in rats and rabbits exposed to 0, 2.5, or 25 ppm (0, 9.5, or 95 mg/m^3) epichlorohydrin 7 hours/day during the critical days of gestation showed no significant differences between controls and treated animals in the incidence of developmental defects, in maternal toxicity, or in histopathology of the lungs, nasal turbinates, or trachea (John *et al.*, 1983b).

Mice and rats (10/sex/concentration/strain) were exposed to 0, 5, 25, or 50 ppm (0, 19, 95, or 190 mg/m^3) epichlorohydrin for 6 hours/day. 5 days/week for 90 days (Quast *et al.*, 1979). Animals were observed for clinical signs of toxicity and were measured biweekly for body weight changes. Body weight measurements, clinical chemistry, hematology, and urinalysis were conducted. Gross and histopathological examinations were performed at the end of the experiment. Exposures of rats to 25 and 50 ppm epichlorohydrin resulted in inflammation, focal erosions, hyperplasia, and metaplasia in the nasal turbinates. No adverse effects were observed in rats exposed to 5 ppm (19 mg/m^3). Mice similarly showed focal erosion, hyperplasia and metaplasia in the epithelium of the nasal turbinates when exposed to 25 ppm epichlorohydrin or greater.

VI. Derivation of U.S. EPA Reference Concentration (RfC)

Study	Quast *et al.* (1979); U.S. EPA (1994)
Study population	Rats and mice (10 per sex per concentration)
Exposure method	Discontinuous whole-body inhalation
Critical effects	Inflammation, focal erosions, hyperplasia, and metaplasia
LOAEL	25 ppm (94.5 mg/m^3)
NOAEL	5 ppm (19 mg/m^3)
Exposure continuity	6 hours/day, 5 days/week
Exposure duration	90 days
Average experimental exposure	0.89 ppm (5 x 6/24 x 5/7)
Human equivalent concentration	0.095 ppm (gas with extrathoracic respiratory effects, RGDR = 0.11, based on MV = 0.14 L, SA(ET) = 11.6 cm^2)
LOAEL factor	1
Subchronic uncertainty factor	10
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.0003 ppm (0.3 ppb; 0.001 mg/m^3; 1 $\mu g/m^3$)

The strengths of the inhalation REL include the availability of controlled exposure inhalation studies in multiple species at multiple exposure concentrations and with adequate histopathogical analysis and the observation of a NOAEL. Major areas of uncertainty are the lack of adequate human exposure data and the lack of chronic inhalation exposure studies, the limited reproductive toxicity data, and the small groups tested in the study.

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CHRONIC TOXICITY SUMMARY

1,2-EPOXYBUTANE

(1-butene oxide; 1,2-butene oxide; 1,2-butylene oxide; 1,2-epoxybutane; 2-ethyloxirane; ethylethylene oxide; NCI-C55527)

CAS Registry Number: 106-88-7

I. Chronic Toxicity Summary

Inhalation reference exposure level	**20 μg/m^3** (U.S. EPA-RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC
Critical effect(s)	Degenerative lesions of the nasal cavity in mice
Hazard index target(s)	Respiratory system; cardiovascular system

II. Physical and Chemical Properties (HSDB, 1997)

Description	Colorless liquid with disagreeable odor
Molecular formula	C_4H_80
Molecular weight	72.12
Density	0.837 g/cm^3 @ 17°C
Boiling point	63.3°C
Vapor pressure	176 mm Hg @ 25°C
Solubility	Soluble in ethanol, ether, acetone, water
Odor threshold	Unknown
Conversion factor	1 ppm = 2.95 mg/m^3

III. Major Uses or Sources

Epoxy butane is used as a chemical intermediate, acid scavenger, and stabilizer for chlorinated solvents (Reprotext, 1994). It is highly reactive, flammable, and undergoes exothermic polymerization reactions in the presence of acids, bases and some salts. It is less volatile than ethylene or propylene oxide (Reprotext, 1994).

IV. Effects of Human Exposure

No human toxicological data were found for 1,2-epoxybutane.

V. Effects of Animal Exposure

F344/N rats (50/sex) were exposed to 0, 200, or 400 ppm EBU for 6 hours/day, 5 days/week for 2 years (NTP, 1988). Survival was impaired and concentration-related increases of inflammation, respiratory epithelial hyperplasia, olfactory sensory epithelial atrophy, and hyperostosis of the nasal turbinate bone cavity were observed in male and female rats exposed to either concentration.

B6C3F1 mice (50/sex) were exposed to 0, 50, or 100 ppm EBU for 6 hours/day, 5 days/week for 2 years (NTP, 1988). Survival and body weight gain were reduced significantly at 100 ppm in both sexes. Significant concentration-related increases in incidence of chronic inflammation, epithelial hyperplasia, and erosion were noted in both sexes at either concentration. Increases in granulocytic hyperplasia and splenic hematopoiesis were noted at both concentrations in female mice.

Male and female mice exposed to 800 ppm (2360 mg/m^3) EBU for 6 hours/day, 5 days/week, for 13 weeks were listless after the first exposure (NTP, 1988). Animals from this group all died by the end of the 13-week exposure. Renal tubular necrosis, and thymic and splenic atrophy were seen in mice exposed to 800 ppm; decreased liver weights were observed following exposure of mice to 400 ppm (1180 mg/m^3) or more. Inflammation of the nasal turbinates was seen in female mice exposed to 100 ppm (295 mg/m^3) or more. No inflammation was observed in controls.

Miller *et al.* (1981) exposed rats and mice of either sex to 0, 75, 150, or 600 ppm (0, 221, 442, or 1770 mg/m^3) EBU 6 hours/day, for 5 days/week. In this study, no treatment-related effects were noted except for histological lesions in the nasal mucosal epithelium and reduced specific gravity in the urine of rats treated with 600 ppm.

Wolf (1961) observed increased lung weights in rats exposed to 800 ppm of a mixture of epoxybutane isomers. No increase in lung weight was seen at 400 ppm.

Sikov *et al.* (1981) conducted experiments to determine the reproductive toxicity of EBU in rats and rabbits. Rats were exposed to 0, 250, or 1000 ppm (0, 738, or 2950 mg/m^3) 1,2-epoxybutane for 7 hours/day, 5 days/week for 3 weeks prior to gestation, or for 7 hours/day on days 1-19 of gestation. Maternal toxicity in the form of 10% weight loss was observed in rats exposed to 1000 ppm. One death out of 42 occurred in the dams exposed to 1000 ppm. No adverse histological, reproductive, or developmental effects were seen at any concentration. Exposure of rabbits on days 1-24 of gestation to the same concentrations as in the rat experiment showed more severe effects at lower concentrations than those observed in rats. In the rabbits, 6 out of 48 dams died during exposure to 250 ppm, and 14 out of 24 died at 1000 ppm. Extensive maternal mortality in this study prevented evaluation of the reproductive and developmental effects.

VI. Derivation of U.S. EPA Reference Concentration (RfC)

Study	National Toxicology Program (NTP, 1988); U.S. EPA, 1994
Study population	Rats and mice
Exposure method	Discontinuous inhalation
Critical effects	Damage to the upper respiratory epithelium was observed in both species at all concentrations. Mice also showed an increased incidence of granulocytic hyperplasia and splenic hematopoiesis at both concentrations, possibly due to inflammation in the upper respiratory tract.
LOAEL	50 ppm (mice)
NOAEL	Not observed
Exposure continuity	6 hours/day, 5 days/week
Exposure duration	2 years
Average experimental exposure	8.9 ppm for LOAEL group (50 x 6/24 x 5/7)
Human equivalent concentration	1.7 ppm for LOAEL group (gas with extrathoracic respiratory effects, RGDR = 0.18, based on MV = 0.06 L, SA(ET) = 2.9 cm^2)
LOAEL uncertainty factor	10
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.006 ppm (6 ppb; 0.02 mg/m^3; 20 $\mu g/m^3$)

The strengths of the inhalation REL include the availability of controlled exposure inhalation studies in multiple species at multiple exposure concentrations and with adequate histopathogical analysis. Major areas of uncertainty are the lack of adequate human exposure data, and the lack of observation of a NOAEL.

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CHRONIC TOXICITY SUMMARY

ETHYLENE

(ethene; acetene; bicarburetted hydrogen; olefiant gas; elayl)

CAS Registry Number: 74-85-1

I. Chronic Toxicity Summary

Inhalation reference exposure level	**20,000 μg/m^3**
Critical effect(s)	Central nervous system impairment
Hazard index target(s)	Nervous system

II. Chemical Property Summary (HSDB, 1997)

Description	Colorless gas; olefinic odor; slightly sweet
Molecular formula	C_2H_4
Molecular weight	28.05
Boiling point	-102.4°C @ 700 mm Hg
Vapor pressure	4270 kPa at 0°C
Solubility	Very slightly soluble in water (131 mg/L H_2O at 20°C). Slightly soluble in acetone, benzene and ethanol. Soluble in diethyl ether
Conversion factor	1.15 μg/m^3 per ppb at 25°C

III. Major Uses and Sources

Ethylene is a petrochemical produced in large quantities worldwide and is ranked 4th in weight made among organic chemicals produced in the U.S. (C&EN, 1995). Over 95% of worldwide annual commercial production of ethylene is currently based on steam cracking of petroleum hydrocarbons. In the U.S. ethane is the primary feedstock to produce ethylene. Commercially produced ethylene is then used as a feedstock for production of polymers and industrial chemicals. A small amount is used for controlled ripening of citrus fruits, tomatoes, bananas and other fruits, vegetables and flowers. Ethylene is ubiquitous in the environment, from both natural and man-made sources. It is a natural product of vegetation of all types and acts as an endogenous plant growth regulator. Endogenous but unidentified sources of ethylene exist in man and animals. A major anthropogenic source is burning vegetation. Ethylene is also released from agricultural wastes and refuse and from the incomplete combustion of fossil fuels. Small amounts are found in volcanic emissions and natural gas. There is little chance of inhalation exposure during its manufacture because the process takes place in a closed system. Exposure may result from spills, leaks or use of ethylene.

Ethylene concentrations of <1-5 $\mu g/m^3$ occur in rural and remote sites while concentrations of 2 to over 1000 $\mu g/m^3$ can occur in urban and indoor sites (IARC, 1994). High indoor concentrations generally depend on whether burning biomass is used as a source of energy. Exposure to ethylene is 10 times greater in cigarette smokers than the exposure in polluted urban air (Persson *et al.*, 1988).

IV. Effects of Human Exposure

The ACGIH considers ethylene to be a simple asphyxiant, an "inert" gas (ACGIH, 1995). Asphyxiants prevent oxygen from combining with hemoglobin. However, ethylene's use in anesthesia in the presence of oxygen indicates that it has inhibitory effects on the human central nervous system (Adriani, 1947; Brumbaugh, 1928; Hunter, 1956).

There is a lack of toxicological data on long-term ethylene exposure in humans. Inhalation pharmacokinetics of ethylene have been performed in human volunteers (Filser *et al.*, 1992). Due to ethylene's poor solubility in blood, the accumulation factor "body/air" at steady-state was determined to be only 0.33±0.13 (mean±SD). The rate of metabolism was directly proportional to the exposure concentration (1st order kinetics) in the range between 1 ppm and 50 ppm. The authors assume that at higher concentrations saturation of human ethylene metabolism occurs, similar to observations in rats (Bolt and Filser, 1987). Only 2% of ethylene inhaled was metabolized to ethylene oxide, whereas 98% of ethylene was exhaled unchanged. The half-life of ethylene was determined to be 0.65 hr. The researchers also determined that the endogenous production of ethylene in the human subjects was 32 nmol/hr.

The measurement of hydroxyethyl adducts to N-terminal valine in hemoglobin has been used as dosimetry for ethylene oxide in occupational studies of fruit store workers exposed to ethylene (Törnqvist *et al.*, 1989). With an average exposure of 0.3 ppm of ethylene, it was estimated from the levels of valine adducts that about 3% of ethylene was metabolized to ethylene oxide. This is in close agreement with studies of ethylene metabolism in human volunteers, which determined an average conversion of 2% inhaled ethylene to ethylene oxide (Filser *et al.*, 1992). Analysis of inhaled ethylene and of adducts from ethylene oxide to N-terminal valine of hemoglobin were performed in 2 smokers to determine the percentage metabolism of ethylene to ethylene oxide due to smoking (Granath *et al.*, 1994). The results were comparable to previous metabolism studies; 2% inhaled ethylene was metabolized to ethylene oxide with a detoxification rate of 1 hr^{-1} for ethylene oxide (corresponding to a $t_{1/2}$ of 42 min).

V. Effects of Animal Exposure

When the body weight and body surface differences between man and rats are taken into account, the pharmacokinetics of ethylene in the two species are similar (Shen *et al.*, 1989). The concentration "body/air" ratio at steady state in rats was 0.54, indicating that accumulation in body tissues does not occur. Ethylene concentrations in rats were highest in fat and lowest in blood after a 12 hour exposure to 300 ppm ethylene (Eide *et al.*, 1995). Twelve hours after cessation of exposure, ethylene was not detectable in the fat. In another pharmacokinetic study

in rats, ethylene metabolism was found to follow first-order kinetics at atmospheric concentrations below 80 ppm (Filser and Bolt, 1984; Bolt and Filser, 1984). Above this range metabolism becomes increasingly saturated, and reaches the maximum metabolic rate (V_{max}) at concentrations of 1000 ppm or more. In view of the saturability of ethylene metabolism, at which is found the maximal possible average body concentration of its metabolite, ethylene oxide, Bolt and Filser (1987) calculated that (theoretical) exposure of rats to ethylene at 40 ppm is equivalent to an ethylene oxide exposure of 1 ppm. However, because of the saturability of ethylene metabolism, ethylene concentrations of 1000 ppm or higher correspond to an ethylene oxide (theoretical) exposure of only 5.6 ppm. In a study of adduct formation among 1-alkenes, ethylene was found to produce a greater amount of hemoglobin and DNA adducts in rats (due to its metabolism to ethylene oxide) than other long-chain 1-alkenes (Eide *et al.*, 1995). In mice, S-(2-hydroxyethyl)cysteine was identified as a metabolite of ethylene in urine (3% of ^{14}C in urine) following inhalation of ^{14}C-ethylene (Ehrenberg *et al.*, 1977).

The available data indicate that ethylene has a low potential for non-cancer chronic toxicity in experimental animals.

In a 13-week inhalation study, 30 Sprague-Dawley rats/group/sex were exposed to 0, 300, 1000, 3000, or 10,000 ppm of ethylene for 6 hr/day, 5 days/week (Rhudy *et al.*, 1978; CIIT, 1977). Body weights, total weight gains and food consumption were not affected in any of the exposed animals. Hematology, clinical chemistry, urinalysis and histopathology did not find any treatment-related effects at any exposure level.

In a comprehensive lifetime inhalation study, 120 Fischer-344 rats/group/sex were exposed to ethylene concentrations of 0, 300, 1000 or 3000 ppm for 6 hr/day, 5 days/week, for up to 24 months (Hamm *et al.*, 1984; CIIT, 1980). Time-weighted average concentrations were 0, 301, 1003, and 3003 ppm. The maximum tolerated dose was not used since concentrations above 3000 ppm were hazardous due to ethylene's explosive properties. Over the 24 months, no differences were noted between exposure groups regarding mortality, clinical blood chemistry, urinalysis, body weights, organ weights or histopathology of a variety of tissues and organs. Inflammatory lesions typical of this strain of rat were distributed equally among all exposure groups.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Hamm et al. (1984)
Study population	Fischer 344 rats (120/sex/group)
Exposure method	Inhalation exposure at 0, 300, 1000 or 3000 ppm
Critical effects	None
LOAEL	Not observed
NOAEL	3000 ppm (free standing)
Exposure continuity	6 hr/d, 5 d/wk
Exposure duration	24 months
Average exposure	535 ppm (3000 x 6/24 x 5/7)
Human equivalent concentration	535 ppm (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation REL for ethylene	18 ppm (20 mg/m^3; 20,000 μg/m^3)

The major strengths of the REL are the availability of long-term animal exposure data on ethylene and the observation of a NOAEL.

Weaknesses of the database for ethylene include the absence of a LOAEL for any toxic effect in the long-term study and a lack of multi-generation studies. Adverse effects on reproduction and development may occur where long-term chronic effects in adults have failed to reveal any toxicity. Rats appear to be tolerant to the long-term effects of ethylene. Toxicity tests in a more ethylene-sensitive experimental animal would strengthen the database for ethylene.

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CHRONIC TOXICITY SUMMARY

ETHYLENE DIBROMIDE

(1,2-dibromoethane; dibromoethane; alpha, beta-dibromoethane; EDB; ethylene bromide; glycol bromide)

CAS Registry Number: 106-93-4

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.8 μg/m^3**
Critical effect(s)	Decreased sperm count/ejaculate, decreased percentage of viable and motile sperm, increased semen pH, and increased proportion of sperm with specific morphological abnormalities in human males
Hazard index target(s)	Reproductive system

II. Chemical Property Summary (HSDB, 1995)

Description	Colorless, heavy, nonflammable liquid with a mildly sweet, chloroform-like odor.
Molecular formula	$C_2H_4Br_2$
Molecular weight	187.88
Boiling point	131-132°C
Vapor pressure	0.11 mm Hg at 20°C
Solubility	Slightly soluble in water, 3400 mg/l water at 20°C. Miscible with most organic solvents.
Conversion factor	7.68 μg/m^3 per ppb at 25°C

III. Major Uses and Sources

Ethylene dibromide (EDB) is used as a solvent for resins, gums and waxes, and as a chemical intermediate in the synthesis of dyes and pharmaceuticals (HSDB, 1995). EDB was once widely used as a fumigant for the control of pests in the U.S. Because of concerns regarding its carcinogenicity, the agricultural uses of EDB were banned in 1983 (RECT, 1988). EDB was also commonly used as a gasoline additive to scavenge inorganic lead compounds. The transition to the use of lead-free gasoline has drastically curtailed the use of EDB in this country (REPROTOX, 1995). EDB is now used mainly in industry. EDB may be formed naturally in the ocean as a result of macro algae growth. Exposure to the general population, via inhalation,

may occur in the vicinity of industries and in industrial settings where this compound is manufactured and used.

IV. Effects of Human Exposures

Pharmacokinetic studies of EDB in humans could not be found in the literature. However, *in vitro* studies of EDB metabolism in human liver samples have been performed (Wiersma *et al.*, 1986). These experiments have shown that the enzyme systems known to metabolize EDB in rodent liver also metabolize EDB in the human liver. EDB was metabolized by human liver cytosolic glutathione S-transferases (GST), microsomal GST, and microsomal mixed function oxidases (MFO). MFO activity resulted in adducts irreversibly bound to protein while GST activity was mostly responsible for adducts irreversibly bound to DNA. Rodent liver enzymes similarly activate EDB to metabolites that bind to cellular macromolecules. In human fetal liver (16-18 weeks gestation) cytosolic GST was also found to metabolize EDB with high efficiency (Kulkarni *et al.*, 1992). Since detoxification via MFO activity may be limited at this stage of development, the results suggest that the human fetus may be at greater risk from EDB toxicity than adults.

A study of mortality from cancer and respiratory diseases was conducted among 161 employees exposed to EDB in 2 production units operated from 1942 to 1969 and from the mid-1920s to 1976, respectively (Ott *et al.*, 1980). No apparent connection was found between mortality due to respiratory diseases and exposure to EDB, when compared to U.S. white male mortality figures.

Due to the structural similarity of EDB to dibromochloropropane (DBCP), a known toxic agent in human male reproductive organs, a number of epidemiological studies concerning male reproduction and spermatogenesis were conducted.

In a study of 59 employees exposed to EDB at the Ethyl Corporation plant in Magnolia, Arkansas, the sperm counts of the exposed men were divided into 2 groups depending on estimated exposure (Ter Haar, 1980). Twenty percent of the low exposure group (<0.5 ppm) had sperm counts below 40 million, whereas 42% of the high exposure group (0.5 to 5 ppm) had sperm counts below this figure. The sperm counts were intermediate between counts reported for 2 types of U.S. samples (for normal men). The observed births among the two exposure groups were found to be similar to the number of expected births. The author determined that EDB had no effect on sterility or reproduction in the workers. Weaknesses of this study include the small population of exposed workers and the lack of a concurrent unexposed control group. Taking these defects of the study into account, Dobbins (1987) concluded that the results provide evidence that EDB exposure between 0.5 and 5.0 ppm is associated with lower sperm counts.

A comparison of observed marital fertility with expected fertility (based on U.S. fertility rates) was conducted among 297 men working at 4 U.S. plants that manufacture EDB (Wong *et al.*, 1979). Fertility was 20% below expected for the four plants combined. This was largely due to plant D, which was 49% below the expected level. After omitting the incidence of vasectomies and hysterectomies among married couples, observed fertility was still 39% below the expected

figure for plant D but was now no longer statistically significant. Exposure levels of EDB at plant D were not known but were estimated to be no more than 5 ppm. Later review determined that expected (control) levels of fertility and the power of the study were too low, resulting in the inability to identify a possible adverse effect (Dobbins, 1987). The lower fertility at plant D indicates that EDB has the potential to reduce fertility, but the extent of the reduction cannot be estimated from this study. Further treatment of the data by a method that uses the proper statistical adjustments of reproductive experience in the U.S. population (used as the control) suggests borderline significance for reduced fertility among the combined workers at the four plants (Wong *et al.*, 1985). The fertility evaluation indicates that more in-depth epidemiologic or physiologic studies are needed.

Semen analysis of 83 pineapple workers at two plantations was performed by Rogers and associates (1981). EDB-exposed workers were removed from each group and placed in a separate group. The remaining two groups of workers acted as control groups. Sperm count, motility and morphology were similar among the three groups. However, 43.8% of exposed workers had abnormally low counts (<40 million/ml) while abnormally low sperm counts of controls were 34.2% and 17.8%. Of the workers that had fertility tests done, 4/4 of the exposed workers tested in the infertile range. Forty percent or less tested in the infertile range among the control groups. The results suggest that workers exposed to EDB had reduced sperm counts, but exposure levels were not known.

Semen analysis among 46 men employed in the papaya fumigation industry was conducted to determine if EDB affected semen quality (Ratcliff *et al.*, 1987; Schrader *et al.*, 1987). Average duration of exposure was 5 years and the geometric mean breathing zone exposure to airborne EDB was 88 ppb (8 hr time weighted average) with peak exposures of up to 262 ppb. The comparison group consisted of 43 unexposed men from a nearby sugar refinery. Following consideration of confounding factors, statistically significant decreases in sperm count/ejaculate, the percentage of viable and motile sperm, and increases in the proportion of sperm with specific morphological abnormalities (tapered heads, absent heads, and abnormal tails) were observed among exposed men. Semen pH was significantly more alkaline than that of unexposed workers. Other measured sperm quality parameters were unchanged. This study suggests that EDB can result in reproductive impairment. However, no measurement of male fertility was conducted.

In a study that examined similar indices of semen quality, 6 week exposure of 10 forestry workers to EDB (60 ppb time weighted average, with peak exposures of up to 2165 ppb) resulted in decreased semen volume and slower sperm velocity (Schrader *et al.*, 1988). Six unexposed men were used as controls. The researchers suggest that short-term exposure to EDB results in decreased sperm velocity while long-term exposure, as in the previous study of EDB-exposed papaya workers, results in sperm immotility and cell death.

V. Effects of Animal Exposures

EDB is readily and rapidly absorbed from the lung when breathed as a vapor, from the GI tract when taken orally, or through the skin when applied dermally (HSDB, 1995). In rats, the rate of absorption of EDB from the respiratory tract reached a plateau within 10 to 20 minutes following exposure to 75 ppm EDB for up to 2 hours (Stott and McKenna, 1984). About 58% of the EDB was absorbed. Intraperitoneal injection of [^{14}C]EDB into guinea pigs resulted in the highest concentrations in liver, kidneys and adrenals (Plotnick and Conner, 1976). Sixty-five percent of the dose was excreted as metabolites in urine, 3% in feces, and 12% excreted unchanged in expired air. In rats, the highest concentrations of [^{14}C]EDB label were found in liver, kidney and spleen following an oral dose of 15 mg/kg body wt (Plotnick *et al.*, 1979). Studies with rats have provided evidence that 2 pathways of metabolic bioactivation exist for EDB (RECT, 1988). The oxidative pathway yields the metabolite 2-bromo-acetaldehyde, which is associated with cell macromolecule binding and liver damage. The conjugative pathway principally yields glutathione products, such as *S*-(2-bromoethyl)-glutathione, which are mainly responsible for DNA binding and mutagenesis. In rats, orally administered EDB is excreted primarily in the urine as mercapturic acid derivatives (Jones and Edwards, 1968). The biologic half-life for elimination of [^{14}C]EDB in rats is 5.1-5.6 hours (Watanabe *et al.*, 1978) and less than 48 hours in mice and guinea pigs (HSDB, 1995). Besides the small amount irreversibly bound to cell macromolecules and DNA, EDB shows little, if any, bioaccumulation in mammalian systems.

In a subchronic toxicity study of experimental animals, rats and guinea pigs were given EDB by oral administration for about 4 months (Aman *et al.*, 1946). Body weights and mortality of animals at or below an average daily dose of 40-50 mg/kg body wt-day were unaffected. However, only one control animal/species was used, the dosing regimen was not well described, and pathologic examination was apparently not performed.

Subchronic exposure of rats (20/sex/group) to 50 ppm EDB for as many as 63 seven-hour exposures in 91 days resulted in no significant change in body weights (Rowe *et al.*, 1952). Liver and kidney weights were increased in both sexes while testis weights were decreased in males. Also, lung weights in males were elevated and spleen weights in females were decreased. Histopathological examination revealed no changes. Guinea pigs (8/sex/group) subjected to as many as 57 seven-hour exposures of 50 ppm EDB in 80 days exhibited reduced body weights. Organ weights were unchanged, but microscopic examination of the livers showed slight central fatty degeneration. In kidneys, slight interstitial congestion and edema with slight parenchymatous degeneration of the tubular epithelium were observed. Four rabbits exposed to 59 seven-hour sessions at 50 ppm in 84 days showed no signs of adverse effects. Clinical signs of monkeys exposed to 50 ppm EDB (49 seven-hour exposures in 70 days) included an ill, unkempt appearance and nervousness. Slight central fatty degeneration in livers was observed, but pathology was not seen in other tissues. Exposure of the same four species to 25 ppm EDB for up to 220 days (145 to 156 seven-hour exposures) showed no signs of adverse effects.

In a 13-week inhalation study, 5 Fischer 344 albino rats/group/sex and 10 B6C3F1 mice/group/sex were exposed to 0, 3, 15 or 75 ppm EDB for 6 hr/day, 5 days/week (Reznik *et al.*, 1980). At 75 ppm, rats and mice exhibited severe necrosis and atrophy of the olfactory epithelium in the nasal cavity. Squamous metaplasia, hyperplasia and cytomegaly of the

epithelium were also seen in nasal turbinals, larynx, trachea, bronchi and bronchioles. Minor alterations were seen in the nasal cavity of only a few male and female rats at 15 ppm. No compound-related lesions were observed in the olfactory and respiratory epithelium at 3 ppm. No lesions were seen in other tissues at any dose.

In another 13-week inhalation study, 40 male and 20 female CDF(F344) rats/group were exposed to 0, 3, 10 or 40 ppm EDB 6 hr/day, 5 days/week (Nitschke *et al.*, 1981). Male rats in the 40 ppm group exhibited decreased weight gain throughout most of the exposure period. However, reduced weight gain was never more than 6-8% below control levels. With the exception of decreased specific gravity of urine in females of the 40 ppm group, no treatment-related changes were observed in any rat group with respect to urinalysis, hematology and clinical chemistry. At the end of 13 weeks, relative liver and kidney weights of males exposed to 40 ppm EDB were significantly elevated while relative liver weights of females in the two highest exposure groups were significantly elevated. Absolute liver weight of females in the 40 ppm group was also significantly elevated. Histopathological examination revealed lesions primarily confined to the anterior sections of the nasal turbinates. Hyperplasia and nonkeratinizing squamous metaplasia of the respiratory epithelium were observed in nasal turbinates of rats exposed to 40 ppm EDB. Only slight epithelial hyperplasia of nasal turbinates was noted at 10 ppm. No treatment related effects were seen at 3 ppm. Livers of females in the 40 ppm group showed a slight increase in fat. After an 88 day recovery period, there was a reversion to normal of the nasal turbinates in all but one rat.

In what was originally scheduled to be a lifetime exposure study, 50 Osborne-Mendel rats/group/sex and 50 B6C3F1 mice/group/sex were administered EDB 5 days/week by gastric - lavage over a substantial portion of their life-span (NCI, 1978). Twenty untreated controls/sex and 20 vehicle controls/sex of each species were included in the study. Rats received initial doses of 80 and 40 mg/kg body wt-day for the first 17 weeks. Due to high mortality, dosing of high dose rats was discontinued for 13 weeks and resumed on week 30 at 40 mg/kg body wt-day. In week 42 all intubations of low and high dose rats ceased for 1 week followed by 4 weeks of dose administration. All surviving, treated male rats were sacrificed in week 49; all surviving, treated female rats were sacrificed in week 61. The resulting time-weighted average dosage over the test period was 38 and 41 mg/kg body wt-day for low and high dose males, respectively, and 37 and 39 mg/kg body wt-day for low and high dose females, respectively. Mice received initial dosages of 120 and 60 mg/kg body wt-day. In weeks 11-13, high and low dosages were increased to 200 and 100 mg/kg body wt-day, respectively. Original dosage levels were resumed after week 13. At week 40, administration of EDB was decreased to 60 mg/kg body wt-day for high dose mice. EDB administration was discontinued at week 54 with sacrifice occurring at week 78 for males and high dose females. Low dose female mice were observed for 37 weeks after intubation ceased. The resulting time-weighted average dosage over the test period was 62 and 107 mg/kg body wt-day for low and high dose mice, respectively. In rats, clinical signs by week 5 included reddened ears and hunched back in all treatment groups. By week 10, all treated rats had reduced body weights ($\geq$10%). Both female and male rats exhibited dose-dependent mortality. Many of the deaths occurred during or shortly after intubation, suggesting an acute toxic reaction. Pathology revealed hyperkeratosis and acanthosis of the forestomach in high dose males and females and in one low dose female. A small number of rats in both treatment groups showed adrenal cortex degeneration and peliosis hepatitis of the liver. Dosed

males showed early development of testicular atrophy. In mice, dose-related body weight reduction and mortality were observed. Clinical signs included alopecia, thin, hunched appearance, soft feces and body sores. Hyperkeratosis and acanthosis of the forestomach were seen in high dose male and female mice. One incidence each of hyperkeratosis (in a female) and acanthosis (in a male) was seen at the low dose. Splenic changes were present in high dose mice and testicular atrophy was present in high dose males.

In a long-term inhalation exposure study, F344 rats and $B6C3F_1$ mice were exposed to 0, 10 or 40 ppm EDB 6 hr/day, 5 days/week for up to 103 weeks (NTP, 1982). In male and female rats, the high dose groups had reduced body weights and increased mortality that began at about week 60. The treatment-related non-neoplastic pathology included hepatic necrosis (both sexes), epithelial hyperplasia and suppurative inflammation throughout the respiratory system (both sexes), and nephropathy (males only). Toxic nephropathy and mineralization were also seen in high dose female rats. Testicular degeneration and atrophy occurred with greater frequency in exposed rats but may be related to observed testicular tumors. Spermatic granulomas were also more frequently seen in high-dose males. Degeneration of the adrenal cortex appeared to be dose-related in females, but only one incidence each was seen in low and high dose males. Increased incidence of retinal atrophy was observed in exposed females. In mice, body weights were reduced at the high dose in both males and females. Many of the high dose animals exhibited a progressive weakness of the limbs or body during the second year. Increased mortality occurred in a dose-related manner in females and was significantly greater in low dose males. Non-neoplastic pathology included epithelial hyperplasia throughout the respiratory system and serous and suppurative inflammation of the nasal cavity in exposed mice. In all male mice, the principal cause of death was urinary bladder inflammation. However, bladder epithelial hyperplasia was only seen in exposed animals. An increased incidence of suppurative inflammation of the prostate was present but was also seen in controls. Dose-related spleen hematopoiesis was observed in females.

Another long-term inhalation study investigated the effects of 0 or 20 ppm EDB (7 hr/day, 5 days/week) on 48 Sprague-Dawley rats/sex/group for 18 months (Wong *et al.*, 1982). Significantly lower body weight gains (>10% difference from controls) occurred by the 15th month in males, and by the 18th month in females. Significantly reduced food consumption was not apparent. Increased mortality rates in both sexes occurred beginning in the 12th month of EDB exposure. All hematological findings were within normal ranges. The only recorded non-neoplastic gross or microscopic finding was atrophy of the spleen in males, which may be related to tumor formation (hemangiosarcoma). The nasal cavity was not examined.

In a study of the effect of EDB on sperm production in bulls (Isreal-Friesian breed), 4 calves were fed 2 mg/kg body wt-day for 12 months (Amir and Volcani, 1965). The bulls were then given EDB in gelatin capsules every other day for 2-4 months longer. EDB did not appear to affect the growth, health and libido of the bulls. However, semen density and motility were significantly lower compared to untreated control bulls of the same age. Many abnormal spermatozoa were also present in treated bulls. A NOAEL for this effect was apparently not determined. Cessation of EDB administration resulted in normal sperm within 10 days to 3 months. Further studies confirmed that EDB adversely affected sperm production without any other apparent effects on bulls (Amir and Volcani, 1967; Amir and Ben-David, 1973). However,

feeding rams 2-5 mg/kg body wt-day for 120 days did not result in any effect on sperm or on the health of the animal (Amir, 1991).

In a developmental toxicity study, 15-17 pregnant Charles River CD rats and 17-19 pregnant CD mice were exposed to 0, 20, 38 and 80 ppm EDB by inhalation 23 hr/day during days 6 to 16 of gestation (Short *et al.*, 1978). A significant increase in mortality occurred in adult rats exposed to 80 ppm EDB and in adult mice exposed to 38 and 80 ppm EDB. Mice exposed to the highest dose experienced 100% mortality. Reduced body weights and feed consumption occurred in both species at all doses tested. Fetal mortality was increased in rats at the highest dose and in mice at 38 ppm. Reduced fetal body weights occurred at 38 ppm in rats and at all exposure levels in mice. No anomalies were seen in rat fetuses. An increase in runts at 38 ppm and a dose-dependent increase in skeletal anomalies were observed among mouse fetuses. However, these anomalies were characteristic of delayed development and occurred at doses that adversely affected maternal welfare. Therefore, these effects are indicative of fetal toxicity rather than teratogenicity.

Male reproductive toxicity of EDB has been evaluated in some other experimental animals. New Zealand white rabbits, dosed subcutaneously with 0, 15, 30 or 45 mg/kg body wt-day, showed adverse effects at the highest dose (Williams *et al.*, 1991). Increased mortality, increased serum enzymes, and liver damage were observed at this dose level. With respect to sperm quality, sperm velocity, motility, and motion parameters were reduced at the highest dose. A dose related decrease in semen pH was also noted. However, male fertility and fetal structural development were unaffected.

In contrast, the dominant lethal assay in mice was negative following a single intraperitoneal injection of 100 mg EDB/kg body wt (Barnett *et al.*, 1992). Germ cell tests did not indicate that EDB was a germ cell mutagen in male mice.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Ratcliff *et al.*, 1987
Study population	46 exposed men, 43 unexposed men; 89 total
Exposure method	Variable workplace breathing zone airborne exposure (88 ppb geometric mean 8-hour time weighted average exposure with peak exposures up to 262 ppb)
Critical effects	Reproductive toxicity; decreased sperm count/ejaculate, decreased percentage of viable and motile sperm, increased semen pH, and increased proportion of sperm with specific morphological abnormalities (tapered heads, absent heads, and abnormal tails) in human males
LOAEL	88 ppb
NOAEL	Not observed
Exposure continuity	8 hr/day (10 m^3/day occupational exposure rate), 5 days/week
Exposure duration	Average, 4.9 years (with standard deviation of 3.6 years)
Average experimental exposure	31 ppb for LOAEL group (88 x 10/20 x 5/7)
Human equivalent concentration	31 ppb
LOAEL uncertainty factor	10
Subchronic uncertainty factor	3
Interspecies factor	1
Intraspecies factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.1 ppb (0.0008 mg/m^3, 0.8 $\mu g/m^3$)

The primary study by Ratcliff and associates (1987) found significant changes in sperm quality indices of papaya workers exposed to EDB vapors for an average of nearly 5 years. No other health effects were apparent. A level of EDB at which no toxicity was observed (NOAEL) was not determined.

In addition to the primary study of Ratcliff *et al.* (1987), several other epidemiological studies strongly suggest a correlation between EDB exposure and male reproductive toxicity (Ter Haar, 1980; Wong *et al.*, 1979; Wong *et al.*, 1985; Rogers *et al.*, 1981; Schrader *et al.*, 1988). This lesion appears to occur in humans at concentrations at which other toxic effects are not seen. EDB also shares some structural similarity to dibromochloropropane (DBCP), a known reproductive toxicant in human males. The evidence for male reproductive toxicity of EDB is not as strong as that for DBCP, probably because EDB is not as potent as DBCP in producing this toxic effect. However, the number of studies indicating a connection between male reproductive toxicity and EDB exposure cannot be ignored for the development of the REL.

Chronic oral exposure of bulls to EDB results in similar toxic effects at low concentrations (equivalent to 0.9 ppm) without affecting the general health of the animal (Amir and Volcani, 1965; Amir, 1991). Unfortunately, a dose-response effect for EDB toxicity, as well as a determination of the NOAEL, has yet to be determined in bulls. Long-term studies of EDB toxicity in other experimental animals suffer from some of the same data deficiencies. Two lifetime studies of EDB exposure in rodents did not yield a NOAEL (NCI, 1978; NTP, 1982). Evidence of testicular atrophy was found in both studies, but at concentrations that also produced toxic effects in other organ systems. The database for chronic toxicity of EDB in experimental animals would be enhanced if the proper doses were chosen to determine a NOAEL.

The strengths of the inhalation REL include the use of human exposure data from workers exposed over a period of years. Major areas of uncertainty are the lack of observation of a NOAEL, the uncertainty in estimating exposure, the potential variability in exposure concentration, and the limited nature of the study (fertility was not actually tested).

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CHRONIC TOXICITY SUMMARY

ETHYLENE DICHLORIDE

(1,2-dichloroethane)

CAS Registry Number: 107-06-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**400 µg/m^3**
Critical effect(s)	Hepatotoxicity; elevated liver enzyme levels in serum of rats.
Hazard index target(s)	Alimentary system; nervous system

II. Physical and Chemical Properties (HSDB, 1995)

Description	Clear, colorless, oily liquid
Molecular formula	$C_2H_4Cl_2$
Molecular weight	98.97
Density	1.2351 g/cm^3 @ 20ºC
Boiling point	83.5ºC
Vapor pressure	64 torr @ 20ºC
Solubility	Slightly soluble in water (0.869 g/100 ml at 20ºC); miscible with alcohol; soluble in ordinary organic solvents
Conversion factor	1 ppm = 4.05 mg/m^3

III. Major Uses or Sources

Ethylene dichloride (EDC) is used primarily in the production of vinyl chloride monomer (HSDB, 1995). It is also an intermediate in the manufacture of trichloroethane and fluorocarbons. EDC has been used as a solvent and a soil fumigant.

IV. Effects of Human Exposure

Nausea, vomiting, dizziness, and unspecified blood changes were reported in a study of workers exposed to levels of 10-37 ppm EDC (Brzozowski *et al.*, 1954). Kozik (1957) reported adverse central nervous systems and liver effects in workers occupationally exposed to concentrations of 16 ppm EDC and below. Nervous system effects were also reported by Rosenbaum (1947) in a study of 100 Russian workers exposed for less than 5 years to concentrations of EDC less than 25 ppm.

Immediately following a 30-minute exposure to an unknown concentration of EDC, a 51 year-old male was somnolent and experienced vomiting (Nouchi *et al.*, 1984). Delirious and trembling, the worker was admitted to the hospital 20 hours post-exposure. The liver was palpable, but serum liver enzymes were normal. The patient lapsed into a coma 3.5 hours following admission to the hospital. A marked elevation in serum liver enzymes was noted on the second day of hospitalization, 35 hours post-exposure. Multiple organ failure occurred on the fourth day of hospitalization and the patient died of arrhythmia. At autopsy, the lungs were congested and edematous. Diffuse degenerative changes were observed in the myocardium. Extensive centrilobular necrosis was observed in the liver and acute centrilobular necrosis was observed in the kidney. Nerve cells in the brain, including Purkinje cells, appeared shrunken with pyknotic nuclei. The latency period for hepatotoxicity of approximately 20 hours suggests that metabolism of the compound yields the reactive agent.

V. Effects of Animal Exposure

Male and female rats (50 per sex) were exposed to 50 ppm EDC 7 hours per day, 5 days per week for 2 years (Cheever *et al.*, 1990). The rats were 5.5-6 weeks of age at the beginning of exposure. No significant increases in any tumor type were observed. Absolute and relative liver weights were not significantly different from controls.

Rats (8-10 per sex per group) were exposed to 0, 5, 10, 50, and 150-250 ppm EDC 7 hours per day, 5 days per week for up to 18 months (Spreafico *et al.*, 1980). Serum chemistry measurements were taken after 3, 6, 12, and 18 months of exposure. Rats to be examined after 3, 6 and 18 months of exposure were 3 months of age at the beginning of the experiment, and rats to be examined after 12 months of exposure were 14 months of age at the beginning of the experiment. No significant changes in serum chemistry parameters were observed at 3, 6, or 18 months of exposure. However, rats exposed to higher levels of EDC for 12 months exhibited changes in serum chemistry indicative of chronic liver damage. Most notably, significant increases in alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and uric acid were observed in addition to significant decreases in cholesterol and aspartate aminotransferase (AST). Blood urea nitrogen (BUN) and γ-glutamyl transpeptidase were also elevated but at non-significant levels. At 150 ppm, similar changes were observed with a statistically significant elevation in BUN. At lower concentrations, AST was significantly elevated while ALT was within normal range. The marked difference between serum chemistry parameters following 12 months of exposure, compared to those following 3, 6 and 18 months of exposure, may be due to the considerable difference in the age of the rats at the start of exposure. This study identifies a 12-month LOAEL of 50 ppm and a NOAEL of 10 ppm in rats.

A study examining the interaction between 1,2-dichloroethane and disulfiram (DSF), a non-carcinogen used extensively in the rubber industry and as a treatment for alcoholism, exposed rats to EDC concentrations of 300 ppm and greater 5 days per week for 30 days (Igwe *et al.*, 1986). Increased liver weights were observed in rats following exposure to 450 ppm EDC (the LOAEL for this study). This study also determined that the interaction

between DSF and EDC greatly increased the toxicity of EDC. Therefore, any person exposed to DSF either occupationally or therapeutically is likely to be more susceptible to the effects of EDC toxicity.

Rats, rabbits, guinea pigs, dogs, cats and monkeys were used in exposures ranging from approximately 100 to 1000 ppm EDC (Heppel *et al.*, 1946). At the highest experimental concentration of 963 ppm, high mortality was observed in rats, rabbits, and guinea pigs following exposure 7 hours per day, 5 days per week for two weeks or less. Guinea pigs exposed to this concentration exhibited lacrimation and inactivity during exposure; pulmonary congestion was noted at autopsy. Rats exposed to this concentration exhibited degenerative proliferative changes in the renal tubular epithelium and splenitis. Pulmonary congestion and focal hemorrhage were also noted in 2 of 4 rats examined. While 4 of 6 cats exposed to this concentration survived until sacrifice 11 weeks following termination of exposure, congestion and fatty infiltration of the liver were observed at necropsy. Due to high mortality in the rodents at the higher concentration, a subsequent experiment exposed rats and guinea pigs 7 hours per day, 5 days per week to 100 ppm EDC for four months. No increase in mortality or effects on growth were observed in rats exposed to this concentration. The rats were successfully bred and their pups were exposed with the dams. No significant findings were observed upon gross and histological examinations of 10/39 exposed and 10 control rats. This study is severely limited by the methods of determining the exposure concentration and by the lack of quantitative measurements of toxicity other than death. This study does however indicate that fatty infiltration of the liver is one indication of toxicity following multiple exposures to EDC.

In a comparative study of the toxicity of EDC, Morgan *et al.* (1990) administered 0, 500, 1000, 2000, 4000, and 8000 ppm in drinking water to several species of rats for 13 weeks. A statistically significant increase in kidney weight was observed in male and female F344/N rats administered 1000 ppm or greater in drinking water. A statistically significant decrease in body weight was observed in rats administered 8000 ppm. Significant decreases in absolute and relative kidney weight were observed in male and female rats administered concentrations of 1000 ppm EDC. A significant increase in relative liver weight was observed in male rats administered 2000 ppm EDC and greater and female rats administered 4000 ppm EDC and greater. Similar but less marked toxicity was observed in the Sprague-Dawley and Osborne-Mendel rats administered 1000 ppm. Additionally, rats were administered EDC in corn oil by gavage at doses of 0, 30, 60, 120, 240, and 480 mg/kg for 13 weeks. Rats administered EDC by gavage exhibited high mortality in the higher dose groups. Statistically significant increases in kidney weights were observed in surviving male rats administered EDC and in female rats administered 120 or 240 mg/kg.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Spreafico *et al*., 1980.
Study population	Rats (8-10 per sex/group)
Exposure method	Discontinuous whole-body inhalation exposures (0, 5, 10, 50, or 150-250 ppm)
Critical effects	Significant elevation in liver enzymes
Exposure duration	12 months
Exposure continuity	7 hours/day, 5 days/week
LOAEL	50 ppm
NOAEL	10 ppm
Average experimental exposure	2.1 ppm for NOAEL group (50 x 7/24 x 5/7)
Human equivalent concentration	3.2 ppm for NOAEL group (gas with systemic effects, based on RGDR = 1.5 for lambda (a) : lambda (h)) (Gargas *et al*., 1989)
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.1 ppm (100 ppb; 0.4 mg/m^3; 400 $\mu g/m^3$)

The strengths of the inhalation REL include the availability of chronic inhalation exposure data, the relatively large number of exposure levels at lower concentrations (allowing for better elucidation of the dose-response relationship for hepatotoxicity), and the observation of a NOAEL.

Major areas of uncertainty are the lack of adequate human exposure data, the lack of reproductive and developmental toxicity studies, the small groups tested in the study, and the lack of multiple-species health effects data.

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CHRONIC TOXICITY SUMMARY

ETHYLENE GLYCOL MONO-N-BUTYL ETHER

(EGBE; butoxyethanol; BE; Butyl Cellosolve®; butyl glycol; butyl glycol ether)

CAS Registry Number: 111-76-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**700 µg/m^3**
Critical effect(s)	Hematological effects in rats
Hazard index target(s)	Cardiovascular system

II. Chemical Property Summary (HSDB, 1997)

Description	Colorless liquid
Molecular formula	$C_6H_{14}O_2$
Molecular weight	118.2 g/mol
Boiling point	171-172°C
Vapor pressure	0.76 mm Hg @ 20°C
Solubility	Soluble in 20 parts water; miscible in most organic solvents
Conversion factor	4.83 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Ethylene glycol mono-n-butyl ether (EGBE) is highly miscible with water and oil and therefore has numerous industrial and household uses as a solvent or cleaner. As of 1983, EGBE was the largest volume glycol ether produced (~10^8 kg/yr, HSDB, 1997). EGBE has uses as a solvent for protective coatings and metal cleaners, a component of hydraulic fluids, a chemical intermediate in the synthesis of di(2-butoxyethyl)phthalate plasticizer and 2-butoxyethyl acetate, and as a coupling agent to stabilize immiscible components of water-based coatings, textile lubricants, and cutting oils.

An approximate breakdown of EGBE use is 41% as a solvent in protective coatings, 18% as a solvent in metal and liquid household cleaners, 10% in the synthesis of 2-butoxyethyl acetate and di(2-butoxyethyl)phthalate, and 31% in other solvent uses (HSDB, 1997).

IV. Effects of Human Exposure

The only studies available which address the toxicity of ethylene glycol monobutyl ether to humans are case reports of toxicity from occupational exposure by inhalation or ingestion and a single study of effects related to short term exposure by inhalation (Carpenter *et al.*, 1956). In that study, six volunteer subjects were exposed to concentrations ranging from 98 to 195 ppm EGBE for 4 or 8 hours. Observations noted at all levels included irritation of the eyes and nose, runny nose, taste disturbances and, in one subject, vomiting. All three subjects exposed to 195 ppm EGBE agreed that this level caused discomfort. Based upon the studies of Werner *et al.* (1943a), in dogs showing increased erythrocyte fragility in vitro, Carpenter also examined erythrocyte fragility in vivo, but did not observe this effect in humans at the EGBE exposure levels studied.

Increased erythrocyte fragility has been observed in rodents following exposure to EGBE (Carpenter *et al.*, 1956). However, recent studies in people found no increase in the fragility of erythrocytes taken from normal and susceptible individuals (persons with hereditary spherocytosis or sickle cell disease and older persons) after a 4-hour incubation with butoxyacetic acid (the presumed EGBE metabolite responsible for hematotoxicity) (Udden, 1994; Udden and Patton, 1994; Ghanayem *et al.*, 1987; Ghanayem, 1989).

V. Effects of Animal Exposure

Experiments were conducted evaluating the toxicity of inhaled EGBE in Fischer 344 rats, including 9-day, and 90-day exposure regimens (Dodd *et al.*, 1983). In the subchronic (90-day) portion of the study, 10 rats/sex/dose group were exposed for 6 hrs/day, 5 days/wk for 13 weeks (66 exposures) to analytical concentrations of 0, 4.7, 25, or 77 ppm EGBE. Another subset of 6 rats/sex/dose group were exposed simultaneously for 6 weeks. No significant effects on body weight, organ weights, clinical chemistry or urine composition were identified, nor were any gross or microscopic lesions. The only significant changes observed were a slight decrease in red blood cells (RBC) among male and female rats and a slight increase in mean corpuscular hemoglobin (MCH) among female rats in the high dose group. Among female rats, the decrease in RBC was more pronounced after 31 complete exposures. Animals (6/sex/dose) in the 9-day study were exposed for 6 hr/day for 5 consecutive days and then for 4 more consecutive days (following a 2 day break) to nominal concentrations of 0, 20, 86, and 245 ppm EGBE. Among animals in the highest dose group audible respiration and nasal discharge were observed during exposure. Weight gain was also depressed in these animals, but returned to normal values during a two week recovery period. Animals in the highest dose group showed hematological toxicity including decreased RBCs, hemoglobin, and mean corpuscular hemoglobin. Decreased hemoglobin was also observed in the 86 ppm dose group, but the effect was not as pronounced as in the highest dose group. No significant changes were observed in the animals exposed to 20 ppm for 9 days.

Dogs (2/group) were exposed to 415 ppm EGBE for 7 hours/day, 5 days/week for 12 weeks (Werner *et al.*, 1943a). Weight losses of 6 and 9% were reported in exposed animals. Hematological effects included decreased hemoglobin, erythrocytes, and hematocrit. Effects

observed, but not quantitated, included increased microcytosis, hypochromia, and polychromatophilia. Changes in hematological parameters in the control animals during the course of the experiment made determination of compound-related effects difficult. The same group reported on the toxicity of EGBE to rats (23/group) exposed to 135 or 320 ppm EGBE for 5 hours/day, 5 days/week for 1, 3, or 5 weeks, including one group sacrificed 1 week post-exposure (Werner *et al.*, 1943b). In both dose groups, erythrocyte count and hemoglobin concentrations were decreased and reticulocyte count was increased.

Rats (4/sex/dose group) were exposed to 0, 20, 50, or 100 ppm EGBE for 15 exposures of 6 hours/day (Gage, 1970). Rats in the 100 ppm EGBE dose group showed increased erythrocyte fragility. No effects were observed in animals in lower dose groups.

Pregnant rats and rabbits (36 and 24 dams/dose group, respectively) were exposed by inhalation to EGBE at concentrations of 0, 25, 50, 100, or 200 ppm on gestational days 6-15 in the rats and 6-18 in the rabbits (Tyl *et al.*, 1984). Maternal toxicity was observed in rats at 100 and 200 ppm EGBE with decreased weight gain, changes in organ weight, changes in food consumption, indications of anemia, and clinical signs including eye wetness and nasal encrustation among the observed adverse effects. Rabbit dams showed signs of toxicity at 200 ppm EGBE, with two deaths reported during the exposure or post-exposure period and decreased weight and some clinical signs including eye and nose wetness and stained fur.

In a study examining the teratological effects from inhalation of 0, 150, or 200 ppm EGBE on pregnant rats, maternal toxicity was observed (Nelson *et al.*, 1984). Animals (N = 18 or 19 with 34 control animals) were exposed for 7 hours/day on gestational days 7-15 and sacrificed on day 20. Hematuria was noted on the first day, but not on subsequent days, in animals exposed to 150 and 200 ppm EGBE. No significant dose-related effects were observed with respect to developmental endpoints.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Dodd *et al.*, 1983
Study population	Rats
Exposure method	Discontinuous inhalation exposure
Critical effects	Decreased red blood cells in females
LOAEL	77 ppm
NOAEL	25 ppm
Exposure continuity	6 hr/day, 5 days/week
Exposure duration	13 weeks
Average experimental exposure	4.5 ppm for NOAEL group (25 x 6/24 x 5/7)
Human equivalent concentration	4.5 ppm for NOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
LOAEL uncertainty factor	1
Subchronic uncertainty factor	10
Interspecies factor	1 (see below)

Intraspecies factor	3 (see below)
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.15 ppm (150 ppb, 0.7 mg/m^3, 700 µg/m^3)

The hematopoietic system toxicity due to inhalation of EGBE has been clearly established from laboratory studies of animals (Dodd *et al.*, 1983; Werner *et al.*, 1943a; Werner *et al.*, 1943b; Gage, 1970; Carpenter *et al.*, 1956). Two studies report NOAELs of 23 ppm EGBE (Dodd *et al.*, 1983) and 50 ppm EGBE (Gage, 1970). The studies of Werner (1943a, 1943b) produced LOAELs of 415 ppm and 135 ppm EGBE, without an observed NOAEL. The lowest NOAEL comes from the study of Dodd *et al.* (1983) showing effects of EGBE on red blood cell levels in a 13-week study. Although only a single dose in the study produced the effect in both sexes (72 ppm EGBE), the shorter term (9 days) study also showed this effect. This value is thus accepted as the basis for the derivation of the chronic REL.

NOAELs of 50 and 100 ppm EGBE were observed in pregnant rats and rabbits exposed by inhalation to EGBE, respectively. Maternal toxicity (decreased weight gain, changes in organ weight, changes in food consumption, hematuria, indications of anemia, etc.) appeared in the 100 and 200 ppm EGBE dose groups (Tyl *et al.*, 1984). The proximity of these levels to those producing hematological effects suggests that both endpoints should be of concern near the chronic REL.

An uncertainty factor of 1 was applied for interspecies extrapolation in light of evidence that humans are not as sensitive as experimental animals for hematological effects of EGBE (Udden, 1994; Udden and Patton, 1994; Ghanayem *et al.*, 1987; Ghanayem, 1989).

An intraspecies uncertainty factor of 3 was used rather than the default value of 10 since the work of Udden (1994) indicates that the blood from patients with hemolytic disorders and from the elderly does not show increased sensitivity to the hemolytic effects of EGBE.

The strengths of the inhalation REL include the availability of controlled inhalation exposure data at multiple exposure concentrations and the observation of a NOAEL. Major areas of uncertainty are the lack of adequate human exposure data and the lack of chronic, multiple-species health effects data.

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CHRONIC TOXICITY SUMMARY

ETHYLENE OXIDE

(oxirane, dimethylene oxide, epoxyethane)

CAS Registry Number: 75-21-8

I. Chronic Toxicity Summary:

Inhalation reference exposure level	**30 μg/m^3**
Critical effect(s)	Neurotoxicity in humans
Hazard index target(s)	Nervous system

II. Physical and Chemical Properties (HSDB, 1995)

Description	Colorless gas
Molecular formula	C_2H_4O
Molecular weight	44.06
Density	1.80 mg/m^3 @ 25ºC
Boiling point	10.7ºC
Vapor pressure	1095 torr @ 20ºC
Conversion factor	1 ppm = 1.80 mg/m^3

III. Major Uses or Sources

The majority of all ethylene oxide (EtO) produced is used as a chemical intermediate in the production of various compounds including ethylene glycol, glycol ethers, and non-ionic surfactants (ATSDR, 1990). EtO is also used as a fumigant for food and cosmetics, and in hospital sterilization of surgical equipment and heat sensitive materials such as plastics.

IV. Effects of Human Exposure

Ten hospital sterilizer workers were matched with controls and examined for physical and neuropsychological health (Estrin *et al.*, 1990). The workers had operated sterilizers using 12% EtO and 88% Freon for an average of 5 years (range 0.5-10 years). Regular monitoring of workroom air had not been done. Measurements at the time of the study indicated concentrations of 15 ppm EtO or less. However, a second measurement showed an air concentration of 250 ppm EtO. A significantly greater percent of exposed workers exhibited a bilateral reflex reduction in the ankle compared to controls. Nerve conduction tests did not identify significant differences between control and exposed workers, but a highly significant reduction ($p = 0.009$) in finger tapping speed was observed in exposed workers. The exposed

group also performed more poorly on tests of spatial and visual abilities, and on tests of visual motor function. The results extended previous work by the same group (Estrin *et al*., 1987).

Cognitive impairment and personality dysfunction were observed more frequently in hospital workers chronically exposed to EtO, compared to a control group (Klees *et al.*, 1990). A group of 22 hospital workers, who had been exposed to an 8-hour TWA of 4.7 ppm EtO for a mean of 6.13 years (range 1-11 years), were matched with 24 control subjects. Neuropsychological function in the workers was classified as normal or impaired on the basis of the questionnaires and of neuropsychological tests by 2 clinical psychologists (who were unaware of exposure status). (If the classification of the two clinicians did not agree, the subject was classified as "disagreement." Disagreement occurred in 7/23 (30%) of the controls and 10/22 (45%) of the exposed.) Exposed subjects were significantly more frequently classified as impaired (5/12) compared to controls (1/16) ($\chi^2 = 6.0861$; $p<0.05$). The Klees *et al*. (1990) study cites several earlier case reports of EtO neurotoxicity.

Recent studies have identified hemoglobin adducts, sister chromatid exchanges, and other hematological effects as indicators of ethylene oxide exposure (Ribeiro *et al.*, 1994; Sarto *et al.*, 1991). However, a recent study of 68 female workers from 9 hospitals in the U.S. and one in Mexico not only reports biological indicators of ethylene oxide exposure, but also provides a complete blood count with differential (Schulte *et al.*, 1995). The workers were classified as low- or high-exposure based on a mean 8-hour time weighted average of 0.08 or 0.17 ppm EtO. The mean length of employment for workers from U.S. hospitals was 5.5 and 10 years for low- and high-exposure workers, respectively. The mean length of employment in low- and high-exposure workers from the hospital in Mexico was 5.9 and 4.2 years, respectively. In workers from U.S. hospitals only, statistically significant decreases in hematocrit and hemoglobin were observed in high-exposure workers compared to low-exposure workers. Also, a statistically significant increase in lymphocytes and a significant decrease in neutrophils were observed in high-exposure workers compared to controls. In the workers from the hospital in Mexico, a significant relationship of EtO exposure and elevated neutrophil count was observed using regression.

At least 2 epidemiological reports indicate a possible association of EtO exposure and spontaneous abortion. Hemminki *et al*. (1982) analyzed spontaneous abortions in Finnish hospital sterilizing staff using data from a postal questionnaire and from a hospital discharge register. The study included all sterilizing staff employed in Finnish hospitals in 1980; the controls were nursing auxiliaries. When the women were involved in sterilizing procedures during their pregnancies, the frequency of spontaneous abortion was 16.7% versus 5.6% for the non-exposed pregnancies. The independent analysis of spontaneous abortions using the hospital discharge register confirmed the findings. Thus two analyses suggested that EtO exposure may carry a risk of spontaneous abortion among sterilizing staff.

More recently Rowland *et al*. (1996) sent questionnaires to 7,000 dental assistants (ages 18-39 years) registered in California in 1987. Of these, 4,856 responded (69%). They analyzed 1,320 women whose most recent pregnancy was conceived while working full-time. Thirty-two reported exposure to EtO; unexposed dental assistants comprised the comparison group. Among exposed women, the age-adjusted relative risk (RR) of spontaneous abortion was 2.5

[95% (CI) = 1.0-6.3]. The RR for pre-term birth was 2.7 (95% CI = 0.8-8.8) and the RR for post-term birth was 2.1 (95% CI = 0.7-5.9). The RR of any of these adverse outcomes among exposed women was estimated to be 2.5 (95% CI = 1.0-6.1). These results also indicate a possible relationship of EtO and spontaneous abortion.

V. Effects of Animal Exposure

A 2 year inhalation bioassay exposed groups of 80 male rats to 0, 50, or 100 ppm EtO 7 hours per day, 5 days per week for 104 weeks (Lynch *et al.*, 1984). Mean body weights were significantly lower and mortality was significantly higher in both exposure groups. Inflammatory lesions of the lung, nasal cavity, trachea and inner ear were observed more frequently in EtO exposed rats. Skeletal muscle myopathy, consisting of atrophy and degeneration of skeletal muscle fibers, was observed more frequently in rats exposed to 100 ppm EtO compared to controls. Neoplastic changes were also observed in EtO exposed rats.

Mice (30 per sex) were exposed to 0, 10, 50, 100, or 250 ppm EtO for 6 hours per day, 5 days per week, for 10 weeks (males) or 11 weeks (females) (Snellings *et al.*, 1984). Neuromuscular screening was conducted, and samples of urine and blood were collected. A significantly greater percent of exposed mice exhibited abnormal posture during gait and reduced locomotor activity. A dose-response was observed for these effects, with significant changes at 50 ppm and greater. An abnormal righting reflex was observed in a significantly greater percent of mice exposed to 100 ppm and above. Reduced or absent toe and tail pinch reflexes were observed in a significantly greater percent of mice exposed to 250 ppm EtO. Hematological changes observed in mice exposed to 250 ppm include slight, yet significant, decreases in red blood cell count, packed cell volume, and hemoglobin concentration. Absolute and relative spleen weights were significantly decreased in female mice exposed to 100 and 250 ppm and in male mice exposed to 250 ppm EtO. A significant increase in relative liver weight was observed in female mice exposed to 250 ppm EtO. Male mice exhibited a significant decrease in body weight at 10, 50, and 250 ppm and a significant decrease in absolute testes weights at 50, 100, or 250 ppm EtO. This study indicates a subchronic NOAEL for neurological effects of 10 ppm EtO.

In a study of the testicular effects of EtO, male rats were exposed to 500 ppm EtO 6 hours per day, 3 days per week for 2, 4, 6, or 13 weeks (Kaido *et al.*, 1992). An awkward gait was observed in rats after 6-9 weeks of exposure. Although no significant changes in body weight were observed, a statistically significant dose-related decrease in testes weight was observed at 4, 6, and 13 weeks of exposure. Progressive degeneration and loss of germ cells were also observed during the 13 week exposure. While severe loss of germ cells and marked morphological changes in remaining germ cells were observed at 6 weeks of exposure, some intact spermatids were observed at 13 weeks of exposure. This suggests that recovery of spermatogenesis occurred.

Saillenfait *et al*. (1996) studied the developmental toxicity of EtO in pregnant Sprague-Dawley rats using inhalation exposure during gestation days 6 to 15. Two protocols were used: (1) exposure for 0.5 hr once a day to 0, 400, 800, or 1200 ppm EtO; or (2) exposure for

0.5 hr three times a day to 0, 200, or 400 ppm EtO or to 0, 800, or 1200 ppm EtO. The second protocol caused fetal toxicity as indicated by reduced fetal weight at 800 ppm (the LOAEL for this endpoint) and at 1200 ppm, and overt maternal toxicity manifested as reduced body weight gain at 1200 ppm. No embryolethality or teratogenicity occurred in either exposure protocol.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Klees *et al*. 1990
Study population	22 hospital workers (and 24 controls)
Exposure method	Workplace exposure
Critical effects	Impaired neurological function
LOAEL	4.7 ppm
NOAEL	Not observed
Exposure continuity	8-hours/day (10 m^3 occupational inhalation rate), 5 days/week
Exposure duration	6.13 years (range 1-11 years)
Average experimental exposure	1.68 ppm (4.7 x 10/20 x 5/7)
Human equivalent concentration	1.68 ppm
LOAEL uncertainty factor	3 (see below)
Subchronic uncertainty factor	3
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	16.8 ppb (30 $\mu g/m^3$)

In the Klees *et al*. (1990) investigation there was a statistically significant difference between controls and exposed. However, one control (out of 16) was judged to be neurologically impaired and less than half the exposed group (5/12) was impaired. The 2 raters could not agree whether a large percent in each group [30% of the controls and 45% of the EtO exposed] was impaired or not. Thus an intermediate LOAEL uncertainty factor was used since less than half the exposed group was adversely affected and the impairment was not conclusive for many subjects.

The strengths of the inhalation REL include the use of human exposure measurements taken from workers who had been working with EtO over a period of years and the use of an endpoint seen in both animals and humans. Use of the neurotoxicologic data in the Snellings *et al*. (1984) subchronic animal study resulted in an estimated chronic REL of 3 $\mu g/m^3$. This is in reasonable agreement with the REL of 30 $\mu g/m^3$ based on human chronic data, when the subchronic to chronic uncertainty factor of 10 used with the animal data is considered.

Major areas of uncertainty are the usual uncertainty in estimating human exposure, the potential variability in exposure concentration, the small number of subjects, the disagreement of the neuropsychologists, and the limited number of developmental toxicity studies.

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CHRONIC TOXICITY SUMMARY

FLUORIDES including HYDROGEN FLUORIDE

(hydrofluoric acid (aqueous solution); hydrogen fluoride (as a gas))

CAS Registry Number: 7664-39-3

I. Chronic Toxicity Summary

Inhalation reference exposure level	**30 μg HF/m^3; 30 μg F/m^3**
Critical effect(s)	Skeletal fluorosis
Hazard index target(s)	Bone; respiratory system

II. Physical and Chemical Properties (HSDB, 1995)

Description	Colorless gas (HF), or as particulates
Molecular formula	HF
Molecular weight	20.0
Density	0.83 g/L @ 25°C
Boiling point	19.51°C
Vapor pressure	400 mm Hg @ 2.5°C
Solubility	Soluble in water and alcohol
Conversion factor	1 ppm = 0.83 mg/m^3 @ 25°C

III. Major Uses or Sources

Hydrofluoric acid (HF) is a colorless, fuming liquid with a sharp, penetrating odor (Fairhall, 1949). This acid is used in the glass etching, electronic and chemical industries (Bertolini, 1992). These industries use HF in the manufacture of such things as metal cans, plastics, refrigerant chemicals, inorganic chemicals, soaps and detergents, high octane gasoline and aircraft parts (Wohlslagel *et al.*, 1976; Wing *et al.*, 1991). Sodium fluoride has been used as a topical and ingested anticaries agent. The optimal doses are not well established, but have been suggested to be approximately 0.080 mg/kg/day for 7 to 9 months old infants decreasing to 0.034 mg/kg/day at 13 years of age (Shulman et al., 1995). A commonly recommended dose of 1.0 mg F ingested per day was reported to reduce dental caries and to be associated with a greatly increased rate of tooth mottling (Van Nieuwenhuysen and D'Hoore, 1992).

IV. Effects of Human Exposure

The chronic exposure to fluorides, including HF, and the incidence of osseous changes were studied in the workplace by Derryberry *et al.* (1963). In this study, the 8-hour time-weighted average fluoride exposure was calculated for the employment period of each of 74 workers. The overall average fluoride exposure in these workers was measured as a time-weighted average of 2.81 mg F/m^3. In comparison, the 17 workers within this group who had evidence of minimally increased bone density had an average fluoride exposure of 3.38 mg F/m^3. The remainder of the workers were exposed to an average measured concentration of 2.64 mg F/m^3. An analysis of these data by OEHHA (see derivation section below) showed a statistically significant relationship between air fluoride and the minimal bone density increases. In addition, urinary fluoride levels were greater in the 17 individuals with greatest exposure compared to the remaining 57 workers (average = 5.18 mg F/L vs. 4.53 mg F/L). No differences between exposed and unexposed individuals were observed for gastrointestinal, cardiovascular, or hematologic systems, or in a physical exam. A significant ($p < 0.05$) increase in the incidence of historical acute respiratory disease was observed in fluoride-exposed individuals, however radiographic examination revealed a difference of lesser significance ($p < 0.10$) for pulmonary changes.

Largent *et al.* (1951) found significant increase in bone density in the lower thoracic spine, with calcification extending into the lateral ligaments of 3 workers exposed for 17, 14, and 10 years to HF (concentrations not estimated).

A group of 74 men, who were occupationally exposed to unspecified concentrations of HF for an average of 2.7 years, reported occasions of upper respiratory irritation (Evans, 1940). Repeated chest X-rays over a 5-year period did not reveal any visible evidence of lung changes. The death rate of these workers from pneumonia and other pulmonary infections was the same as that of unexposed plant employees.

The possible effects of HF on a population of 47 workers exposed to HF (concentrations unspecified) included back pain and stiffness, cervical spine, knee pain, and shortness of breath on exertion (Peperkorn and Kahling, 1944). Many workers had external HF burn scars and rigidity in the chest. Radiologic examination revealed skeletal fluorosis in 34 of the 47 workers. The first evidence of these osseous changes was in the pelvis and lumbar spine, followed by changes in the spinal column and ribs. Extremities were affected last. The degree of radiologic changes increased with duration of employment. First-degree radiologic changes (increased bone density and thickened and misshapen structure of the trabeculae with the marginal contours of the bones exhibiting slight blurring) were observed no sooner than after 3 years of employment. More severe changes took at least 7 years of employment to manifest.

Workers in a warehouse containing HF retorts experienced transitory hyperemia (Dale and McCauley, 1948). Twenty four of the 40 workers had definite changes in the thickness and number of trabeculae in the upper and lower jaw.

Examinations of 107 pot room workers in two aluminum plants with airborne fluorides revealed 22 subjects with limited motion of the dorsolumbar spine, compared with none in a control group of 108 workers with no history of exposure to fluorides (Kaltreider *et al.*, 1972).

In one plant, 76 of 79 workers had increased bone density as measured by roentgenogram, with diagnosis of slight to moderate fluorosis. Moderate and marked fluorosis was observed after 15 years employment. The 8-hour time-weighted average fluoride content in these workplaces was 2.4 to 6.0 mg/m^3. Balazova (1971) measured significant fluoride uptake and distribution in children living near an aluminum smelter but reported no incidence of fluorosis.

Oral supplementation of greater than 0.1 mg F/kg body weight daily has been associated with fluorosis (Forsman, 1977).

Fluoride ion produced by various fluorocarbons has been associated with toxicity to human kidney collecting duct cells leading to sodium and water disturbances (Cittanova et al., 1996).

V. Effects of Chronic Exposures to Animals

Stokinger (1949) studied the subchronic effects of HF inhalation in several animal species. Animals (dogs, rabbits, rats, guinea pigs, and mice; 1 to 6 per group) were exposed to 0, 7.2 mg/m^3, or 25.1 mg/m^3 6 hours/day, 6 days/week, for 30 days. Mortality, body weight, blood coagulation mechanisms, and gross pathology were measured. Exposure to 25.1 mg/m^3 for 30 days resulted in degenerative testicular changes and ulceration of the scrotum in all 4 dogs and hemorrhage and edema in the lungs of 3 dogs. Pulmonary hemorrhage was also seen in 20 of 30 rats, and 4 of 10 rabbits. Renal cortical degeneration was observed in 27 of 30 rats. All of the rats and mice at the 25.1 mg/m^3 concentration died. No mortality was observed in the other species tested. Blood fibrinogen levels were significantly increased in dogs, rats and rabbits exposed to 25.1 mg/m^3. Exposure to 7.2 mg/m^3 resulted in pulmonary hemorrhage in 1 out of 5 dogs. No other significant effects were observed at the lower concentration.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Derryberry *et al.* (1963)
Study population	74 fertilizer plant workers (67 unexposed control subjects)
Exposure method	Occupational
Critical effects	Increased bone density (skeletal fluorosis)
LOAEL	1.89 mg F/m^3 (2.46 mg HF/m^3)
NOAEL	1.07 mg F/m^3 (1.13 mg HF/m^3)
Exposure continuity	8 hours/day, 5 days/week
Exposure duration	14.1 years (range = 4.5 to 25.9 years)
Average exposure concentration	0.27 mg HF/m^3 or 0.26 mg F/m^3
Human equivalent concentration	0.27 mg HF/m^3 or 0.26 mg F/m^3
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1

Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Inhalation reference exposure level for F or HF	0.03 mg HF/m^3 (30 μg HF/m^3; 0.04 ppm; 40 ppb) 0.03 mg F/m^3 (30 μg F/m^3; 0.04 ppm; 40 ppb)

No studies regarding the chronic irritant or respiratory effects of HF exposure in humans or animals were available.

Changes in bone density in association with fluoride exposure have been observed in several studies, and appear to be the most sensitive health effect for chronic exposure. The minimally increased bone density in the Derryberry study was significantly ($p < 0.04$, Fisher's Exact Test) associated with "other osseous changes" which reportedly included disc lesions, arthritis, and calcified ligaments. An increase in pulmonary changes in the workers with high bone density was marginally significant ($p < 0.06$) and included emphysema, fibrosis, and healed tuberculous lesions. Although dental fluorosis is a sensitive endpoint in many fluoride studies, the dental examinations of exposed workers in this study showed healthier teeth than in controls. The increased bone density observed was considered as indicating adverse effects had occurred, based on the adverse effects associated with the increased density in the study, and on research showing increased bone density caused by fluoride exposure also leads to decreased bone strength and increased fragility (Riggs *et al.*, 1990). Symptoms of abdominal pain, backache, restricted joint movement and respiratory symptoms have been associated with airborne fluoride exposures and bone density increases in industrial settings (Zhiliang et al., 1987).

The absorption of particulate and gaseous fluorides is reported to be similar (Collings *et al.*, 1951). Therefore, it would be expected that the effects on bone density would be similar regardless of the form of fluoride. The raw data from the Derryberry *et al.* (1963) study are shown in Table 1. A Pearson correlation matrix of the variables measured in the Derryberry *et al.* study indicated that bone density was best correlated with mean air fluoride level, and to a lesser extent with the age of the individual. A log-logistic regression using the log air fluoride concentration as the independent variable showed a significant ($p < 0.033$) relationship between increasing air fluoride concentrations and probability of skeletal fluorosis. The parameters for the regression were $\beta_0 = -2.3468$ (std. error = 0.6462), and $\beta_1 = 1.1736$ (std error = 0.5508); the odds ratio for the occurrence of skeletal fluorosis was 3.24. Years of exposure were not correlated with increased bone-density, according to a Pearson Correlation procedure ($p = 0.63$). Bone density has been shown to decrease with age after the age of 40 among normal, non-fluoride-exposed males (Runge *et al.*, 1979). As expected, age was very highly correlated with years exposed ($p<0.00001$), therefore including years exposed in the dose-metric likely introduces a confounding variable. Similarly, Runge *et al.* (1979) found no association between years exposed and mineral content or bone width among 245 aluminum smelter workers exposed to 2.75 or 3.2 mg F/m^3. For these reasons, years exposed were not used as the dose-metric for bone-density in this analysis.

Although a threshold was not readily apparent from the logistic regression model, grouping the 74 individuals by air fluoride exposure level into quintiles of 15 each with one group of 14, allowed for a comparison of group mean responses (Table 2). The 14 employees exposed

to a time-weighted average concentration of 1.07 mg F/m^3 did not exhibit bone density changes. An analysis of the grouped responses using a binomial distribution showed a probability of p = 0.008 for obtaining 4/15 increased bone density observations in the 2.34 mg/m^3 group, and a probability of p = 0.047 for obtaining 3/15 positive observations in the 1.89 mg F/m^3 group. The 1.89 mg F/m^3 group was therefore considered a LOAEL for chronic skeletal fluorosis, and the 1.07 mg/m^3 group was considered a NOAEL. The above probabilities assume that a chance occurrence is, at most, 1 in 18 of skeletal fluorosis or other cause leading to an abnormally dense x-ray in the general population. Since osteosclerosis is a rare condition that is associated with several types of hematological malignancies such as myeloid leukemia, the actual incidence of conditions leading to osteosclerosis is far below 1 in 18. This lends strong support to the consideration of 1.89 mg/m^3 as a LOAEL for skeletal fluorosis.

The major strengths of the key study are the observation of health effects in a large group of workers exposed over many years, the availability of individual exposure estimates for each worker, and the identification of a NOAEL. The primary uncertainty in the study is the lack of a comprehensive health effects examination. Another source for potential concern is the relative susceptibility of children to the effects of inhaled fluorides, considering the rapid bone growth in early years. Although a number of studies were located that compared children and adult responses to environmental sources of fluorides, none of the differences in fluorosis were of a sufficient magnitude to warrant a greater than 10-fold uncertainty factor for individual susceptibility.

Table 1. Data on worker exposure to fluoride from Derryberry *et al.* (1963)

Obsv. #	ID	Bone density	Years exposed	Urine max F (mg F/L)	Urine min F (mg F/L)	Mean urinary F (mg F/L)	Age (years)	Air fluoride (mg/m^3)	*OEHHA exposure grouping*
1	119	normal	18.5	43.0	2.8	14.7	58	8.16	5
2	0	normal	8.4	24.7	5.3	9.6	42	3.19	4
3	41	normal	15.8	35.0	2.5	9.1	35	3.29	4
4	147	minimally increased	9.6	17.1	2.1	8.9	60	5.98	5
5	120	normal	16.7	20.5	3.4	8.6	55	3.29	4
6	54	minimally increased	17.0	44.0	4.0	8.6	56	7.73	5
7	148	normal	10.5	14.0	3.7	8.4	41	8.32	5
8	314	minimally increased	14.4	22.7	1.7	8.3	56	3.24	4
9	29	normal	17.0	18.2	2.5	7.7	50	2.60	3
10	14	normal	14.3	19.4	2.1	6.3	46	2.33	3
11	115	normal	15.2	18.5	1.4	6.3	38	2.11	3
12	10	minimally increased	10.3	22.0	2.3	6.1	38	2.72	4
13	4	minimally increased	7.1	7.7	2.0	5.7	54	3.22	4
14	51	normal	14.9	42.0	0.8	5.6	46	3.18	4
15	94	normal	16.2	15.4	3.3	5.5	56	5.12	5
16	217	normal	7.1	7.1	2.6	5.3	42	2.54	3
17	281	minimally increased	7.8	8.6	1.1	5.2	36	3.79	4
18	114	normal	10.4	13.2	2.8	5.2	38	7.66	5
19	7	normal	7.8	9.1	2.2	5.1	43	2.91	4
20	308	normal	11.9	6.7	3.5	5.1	44	1.89	2
21	301	minimally increased	15.2	9.5	2.5	5	36	2.56	3
22	72	normal	25.9	13.7	2.1	4.9	55	5.55	5
23	241	minimally increased	17.0	10.0	1.9	4.9	46	4.48	5
24	345	normal	10.5	7.1	2.0	4.9	47	1.49	1
25	26	normal	16.4	12.2	0.5	4.7	39	2.41	3
26	231	minimally increased	16.3	8.2	2.8	4.6	62	1.88	2
27	2	normal	24.7	8.9	2.1	4.6	46	3.53	4
28	295	normal	14.5	10.7	0.9	4.6	44	2.07	3
29	1	normal	8.9	5.9	2.4	4.5	30	1.92	2
30	203	minimally increased	18.2	6.8	1.6	4.4	43	2.66	3
31	63	normal	16.2	7.4	2.0	4.3	55	3.90	5
32	5	normal	4.5	11.5	1.9	4.3	43	1.12	1
33	460	normal	12.5	6.1	1.6	4.3	60	2.13	3
34	249	minimally	15.0	8.0	1.8	4.3	39	2.95	4

		increased							
35	3	normal	7.6	14.5	2.1	4.3	31	3.90	5
36	322	normal	9.3	6.3	2.0	4.3	35	4.23	5
37	8	minimally increased	24.8	5.9	3.0	4.2	55	2.50	3

Observation	ID	Bone density	Years exposed	Urine max F (mg F/L)	Urine min F (mg F/L)	Mean urinary F (mg F/L)	Age (years)	Air fluoride (mg F/m^3)	*OEHHA exposure grouping*
38	3	normal	15.2	12.2	2.1	4.2	42	1.14	1
39	309	normal	12.1	5.5	2.4	4.1	42	1.94	2
40	36	normal	9.1	13.2	0.8	4.1	33	1.94	2
41	45	normal	11.3	14.0	2.2	4.1	33	3.84	4
42	70	normal	17.9	8.0	1.0	3.9	44	4.00	5
43	250	minimally increased	9.8	6.7	1.5	3.9	35	1.78	2
44	38	normal	16.9	5.9	1.0	3.9	35	2.10	3
45	200	minimally increased	14.0	7.0	2.8	3.8	66	3.92	5
46	183	normal	9.8	4.9	2.2	3.7	48	1.67	2
47	32	normal	12.5	6.6	0.9	3.7	47	2.21	3
48	25	normal	13.6	5.5	1.5	3.7	44	1.86	2
49	21	normal	13.9	9.1	0.4	3.7	50	1.98	2
50	304	normal	13.4	5.0	2.1	3.7	36	2.62	3
51	132	normal	10.9	5.1	2.4	3.6	39	1.81	2
52	6	minimally increased	8.4	4.8	0.9	3.6	35	3.85	5
53	244	normal	16.6	7.1	1.4	3.6	62	2.87	4
54	30	normal	14.0	14.0	0.9	3.6	43	1.56	1
55	88	minimally increased	15.5	4.9	1.7	3.5	66	2.06	2
56	227	normal	16.6	5.7	1.0	3.5	41	1.18	1
57	271	normal	17.7	4.1	3.0	3.4	60	1.82	2
58	19	normal	13.9	10.0	1.8	3.4	41	1.32	1
59	190	normal	9.3	7.7	1.9	3.3	36	1.95	2
60	258	normal	17.8	5.6	1.6	3.2	58	0.87	1
61	278	normal	10.0	7.0	0.3	3.2	34	1.93	2
62	331	normal	12.8	5.6	1.5	3.1	34	1.23	1
63	91	normal	25.3	7.9	0.2	3.1	63	3.49	4
64	342	normal	18.5	6.0	1.3	3	40	2.73	4
65	261	normal	18.1	5.3	0.9	2.9	52	4.41	5
66	291	normal	13.5	4.5	1.5	2.8	34	2.14	3
67	149	normal	11.3	4.5	2.1	2.8	34	0.76	1
68	2	normal	24.7	4.5	1.5	2.7	51	1.15	1
69	4	normal	16.8	5.7	1.2	2.7	56	0.71	1
70	109	normal	8.3	5.1	0.8	2.7	36	1.89	2
71	242	normal	18.1	4.1	1.2	2.5	49	1.26	1
72	179	normal	18.9	3.9	1.0	2.4	46	0.50	1
73	325	minimally increased	11.8	5.0	0.5	2.2	40	2.10	3
74	159	normal	18.9	5.0	0.7	2.1	45	0.67	1

Table 2. Grouped mean exposure

Exposure group	Mean age ± SD	Mean air level mg F/m^3 ± SD	Number of responses	Probability of difference from group 1*
1	45.0 ± 7.0	1.07 ± 0.32	0/14**	Not Applicable
2	43.9 ± 11.2	1.89 ± 0.09	3/15***	0.047
3	43.0 ± 7.6	2.34 ± 0.23	4/15	0.008
4	45.9 ± 9.8	3.22 ± 0.35	5/15	0.001
5	48.5 ± 10.7	5.41 ± 1.72	5/15	0.001

* Probability of obtaining result assuming a chance occurrence of abnormally dense x-ray of, at most, 1 in 18 individuals, using a binomial distribution (Systat for Windows v.5.05, 1994).
** NOAEL
*** LOAEL ($p < 0.05$)

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CHRONIC TOXICITY SUMMARY

GLUTARALDEHYDE

(1,5-pentanedial; 1,5-pentanedione; glutaric dialdehyde; Aldesen; Cidex; Sonacide)

CAS Registry Number: 111-30-8

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.1 µg/m^3**
Critical effect(s)	Neutrophilic infiltration in the olfactory epithelium of the respiratory system of mice
Hazard index target(s)	Respiratory system

II. Chemical Property Summary (HSDB, 1996)

Description	Colorless liquid
Molecular formula	$C_5H_8O_2$
Molecular weight	100.13
Boiling point	187-189°C
Vapor pressure	17 mm Hg @ 20°C
Solubility	Soluble in water, alcohol, benzene
Conversion factor	4.1 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Glutaraldehyde is a chemical frequently used as a disinfectant and sterilizing agent against bacteria and viruses (2% solution), an embalming fluid and tissue fixative, a component of leather tanning solutions, and an intermediate in the production of certain sealants, resins, dyes, and electrical products (HSDB, 1996). For commercial purposes, solutions of 99%, 50%, and 20% are available.

IV. Effects of Human Exposure

Evidence of the toxicity of glutaraldehyde to humans is limited to reports of occupational exposure from its use as a disinfectant and sterilizing agent. Frequently observed effects from exposure include skin sensitivity resulting in dermatitis, and irritation of the eyes and nose with accompanying rhinitis (Jordan *et al.*, 1972; Corrado *et al.*, 1986; Hansen, 1983; Wiggins *et al.*, 1989). Occupational asthma has also been reported among workers repeatedly exposed to glutaraldehyde, particularly respiratory technologists who use glutaraldehyde as a sterilizing agent for endoscopes (Chan-Yeung *et al.*, 1993; Stenton *et al.*, 1994; Gannon *et al.*,

1995). No studies addressing glutaraldehyde sensitivity from chronic exposure include the quantitation of the exposure levels that led to the sensitization.

V. Effects of Animal Exposure

The histopathology of the respiratory tract in rats and mice exposed to glutaraldehyde by inhalation was examined (Gross *et al.*, 1994). F344 rats and B6C3F1 mice (20 animals of each sex and of each species at each exposure level for a total of 480 rodents) were continuously exposed to glutaraldehyde in recirculating exposure chambers at concentrations of 0, 62.5, 125, 250, 500, or 1000 ppb glutaraldehyde for one day, 4 days, 6 weeks, or 13 weeks. At termination, respiratory tract tissue as well as duodenum and any gross lesions were collected and formalin fixed. Animals were treated with tritiated thymidine two hours before termination to evaluate cell replication in certain respiratory tract tissues. Respiratory tract tissue sections were made as follows: transverse sections of the nose and trachea, frontal section of the carina, and longitudinal section of the lung. Ten male and 10 female mice exposed to 1000 ppb and one female mouse exposed to 500 ppb group died during the course of the study. Two male and 3 female rats exposed to 1000 ppb died during the course of the study. Histopathological examination of animals surviving to the end of the study entailed scoring the severity of the finding from "no response" to "very severe" response on a 0 to 5 scale. Unit length labeling index, the indicator of cell proliferation, was evaluated by autoradiography at two sites: the nasal vestibule and the dorsal atrioturbinate.

Lesions in animals treated with glutaraldehyde appeared primarily in the anterior third of the nose. Lesions were apparently more increased in mice compared to rats due to some level of "background" non-suppurative lesions in the rats. Mice were considered devoid of background lesions. In the 13-week study, female mice were the most sensitive, with lesions averaging a score of 2 (mild and clear, but of limited extent and/or severity). The lesions were characterized as neutrophilic infiltration primarily in the squamous epithelium of the vestibule, with thickening of the epithelium leading to loss of the characteristic surface grooves. Both cell size and number were reported to be increased. Lesions were generally found to increase in nature and severity with increased time and level of exposure. Obstruction of the nasal vestibule was thought to account for the mortality of animals in the higher dose groups. In female mice at 13 weeks, all glutaraldehyde dose groups showed the accumulation of eosinophilic proteinaceous deposits in the respiratory epithelium of the maxilloturbinate margin. Examination of unit length labeling indices as a measure of growth showed significant increases in all treated groups of female mice. No evidence of exposure related lesions was found in the respiratory tract in the trachea, carina, bronchi, or lungs.

Greenspan *et al.* (1985) exposed male and female F-344 rats to 0, 0.3, 1.1 and 3.1 ppm glutaraldehyde and 0, 0.2, 0.63, and 2.1 ppm glutaraldehyde, respectively, in a 9-day study, and both sexes to 0, 21, 49, and 194 ppb glutaraldehyde in a 14 week study. Animal numbers were not specified. Exposures were conducted for 6 hours per day, 5 days per week. In the 9-day study, observations in the high and intermediate dose level groups included reduced body weight gain, inflammation of the nasal and olfactory mucosa, and sensory irritation. In the two highest doses of the 14-week study, statistically significant differences in body weight

gain were observed as well as perinasal wetness. No histopathological indication of inflammation in olfactory or nasal mucosa was observed.

Mice were exposed to 0, 0.3, 1.0, and 2.6 ppm glutaraldehyde vapors for 6 hours/day for 4, 9, or 14 days (Zissu *et al.*, 1994). These mice were killed immediately after the exposure period. Other groups exposed to 1.0 ppm for 14 days were killed after recovery periods of 1, 2, and 4 weeks. After 4 days of exposure to the lowest dose, mice showed lesions in the respiratory epithelium of the septum, and the naso- and maxilloturbinates. After exposure to 1.0 ppm glutaraldehyde, lesions were still judged as severe after 2 weeks of recovery.

A study comparing the effects of intra-nasally instilled glutaraldehyde and formaldehyde on rat nasal epithelium found inflammation, epithelial degeneration, respiratory epithelial hypertrophy, and squamous metaplasia in treated animals (St. Clair *et al.*, 1990). Acute inhalation exposure to formaldehyde produced identical lesions. Ten-fold higher concentrations of instilled formaldehyde were required to produce the same effect as instilled glutaraldehyde.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Gross *et al.*, 1994
Study population	Male and female F344 rats and B6C3F1 mice (20/sex/group)
Exposure method	Continuous inhalation exposure (0, 62.5, 125, 250, 500, or 1000 ppb)
Critical effects	Neutrophilic infiltration in olfactory epithelium
LOAEL	62.5 ppb (female mice)
NOAEL	Not observed
Exposure continuity	24 hr/day, 7 days/week
Exposure duration	13 weeks
Average experimental exposure	62.5 ppb
Human equivalent concentration	10.5 ppb (gas with extrathoracic respiratory effects, RGDR = 0.17, BW = 28 g, MV = 0.032 L/min, SA = 3 cm^2)
Subchronic uncertainty factor	3
LOAEL uncertainty factor	3
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.035 ppb (0.1 $\mu g/m^3$)

Several studies indicate that the upper respiratory tract is a target for the toxicity of glutaraldehyde from inhalation exposure. Reports of toxicity to humans show that exposure can lead to occupational asthma as well as cause irritation of the eyes and nose with accompanying rhinitis. Likewise, animals exposed to glutaraldehyde by the inhalation route show evidence of respiratory irritation with the induction of lesions of the anterior nasal

cavities upon long-term exposure (Gross *et al.*, 1994; Greenspan *et al.*, 1985). The most thorough reporting of this effect is the study by Gross *et al.* (1994) showing neutrophilic infiltration in the olfactory epithelium in the lowest dose exposure group. (Female mice exposed to 62.5 ppb showed subepithelial neutrophilic infiltration.) This level was taken to be the LOAEL. This effect on the nasal epithelium was demonstrated to be both concentration- and exposure duration-dependent.

The major strength of the inhalation REL is the availability of controlled exposure inhalation studies in multiple species at multiple exposure concentrations and with adequate histopathogical analysis. Major areas of uncertainty are the lack of human data, the lack of chronic inhalation exposure studies, the lack of reproductive and developmental toxicity studies, the lack of dermal sensitization studies, and the lack of observation of a NOAEL.

VII. References

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CHRONIC TOXICITY SUMMARY

HYDRAZINE

(diamine; diamide; nitrogen hydride; levoxine)

CAS Registry Number: 302-01-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.2 µg/m^3**
Critical effect(s)	Amyloidosis of the liver and thyroid in hamsters
Hazard index target(s)	Alimentary system; endocrine system

II. Chemical Property Summary (HSDB, 1995)

Molecular formula	N_2H_4
Molecular weight	32.05 g/mol
Description	Colorless, oily liquid; white crystals
Boiling point	113.5°C (Merck, 1983)
Melting point	2°C
Vapor pressure	14.4 mm Hg @ 25°C
Solubility	Miscible with water, methyl-, ethyl-, isobutyl alcohols; slightly miscible with hydrocarbons; insoluble in chloroform, ether
Conversion factor	1.31 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Hydrazine is a highly reactive base and reducing agent. Its primary uses are as a high-energy rocket propellant, as a reactant in military fuel cells, in nickel plating, in the polymerization of urethane, for removal of halogens from wastewater, as an oxygen scavenger in boiler feedwater to inhibit corrosion, and in photographic development (Von Burg and Stout, 1991). Hydrazine was historically used experimentally as a therapeutic agent in the treatment of tuberculosis, sickle cell anemia, and non-specific chronic illnesses (Von Burg and Stout, 1991; Gold, 1987).

IV. Effects of Human Exposure

One person was occupationally exposed to hydrazine at unknown levels once per week for a period of 6 months (Sotaniemi *et al.*, 1971). The worker showed symptoms of conjunctivitis, tremors, and lethargy for 1-2 days following each exposure. Vomiting, fever, and diarrhea developed on the last day of exposure which progressed to abdominal pain and incoherence. The previously healthy 59-year old individual died three weeks after the last exposure. Evidence of tracheitis, bronchitis, heart muscle degeneration, and liver and kidney damage were found at autopsy. A single case report can not prove a cause and effect relationship between hydrazine exposures and the noted symptoms and death, but the repeated association between exposures and symptoms is highly suspicious.

The only epidemiological studies of human hydrazine exposures found involve workers in a hydrazine manufacturing plant (Wald et al., 1984; Wald, 1985; Morris et al., 1995). Workers were exposed to various durations of at least 6 months between 1945 and 1972 and have been followed through 1992. The studies are based on a review of medical records. Only 78 of 427 workers were believed to have had more than incidental exposure to hydrazine. Only cumulative mortality was reviewed. Health effects reported during or after hydrazine exposure were not examined. No increase in mortality was noted for lung cancer, other cancers, or causes other than cancer. However, these small studies have little power to detect increased mortality, and age of death was not examined. The authors reported that relative risks up to 3.5 could have gone undetected.

Dermal sensitization has also been reported from repeated contact with hydrazine (Van Ketal, 1964; Von Keilig and Speer U, 1983; Wrangsjo and Martensson, 1986).

V. Effects of Animal Exposure

An inhalation study of the toxicity and carcinogenicity of hydrazine was conducted in cats, mice, hamsters, and dogs (Vernot *et al.*, 1985). Various animal groups were exposed 6 hours/day, 5 days/weeks for one year to concentrations of 0.05, 0.25, 1.0, and 5.0 ppm anhydrous hydrazine base. Exposed and controls groups were made up of the following animals: 100 Fischer 344 rats/sex at 0.05, 0.25, 1.0 and 5.0 ppm hydrazine plus 150 rats/sex as controls; 400 female C57BL/6 mice at 0.05, 0.25, and 1.0 ppm hydrazine plus 800 female mice as controls; 200 male Golden Syrian hamsters at 0.25, 1.0, and 5.0 ppm hydrazine plus 200 male hamsters as controls; 4 beagle dogs/sex at 0.25 and 1.0 ppm hydrazine plus 4 dogs/sex as controls. Animals were observed post-exposure for the following periods: 18 months for rats, 15 months for mice, 12 months for hamsters, and 38 months for dogs. Animals were observed hourly during the exposure period and daily in the post-exposure period.

No non-cancer toxic effects were observed in mice or dogs, with the exception of a single dog exposed to 1.0 ppm hydrazine which showed cyclic elevations in serum glutamic-pyruvic transaminase levels and, upon necropsy at 36 months post-exposure, showed liver effects described as “clusters of swollen hepatocytes that had highly vacuolated cytoplasm”. Of the other species examined, hamsters showed toxicity at the lowest dose levels, particularly amyloidosis in various organs including liver, spleen, kidney, thyroid, and adrenal glands. An

increased incidence of amyloidosis was seen at the lowest exposure level (0.25 ppm hydrazine) in the liver and thyroid (67/160 exposed vs. 42/180 control for the liver and 20/117 exposed vs. 15/179 control in the thyroid; $p \leq 0.01$ by Fisher's exact test). This effect was found to be dose related. The incidence of hemosiderosis of the liver was also significantly increased in all exposed groups. Significantly increased incidences of toxic effects observed in the 1.0 and 5.0 ppm hydrazine groups include amyloidosis of the spleen, kidney glomerulus, and adrenals glands, and lymphadenitis of the lymph nodes. Significantly increased toxic effects observed only in the highest dose group include amyloidosis of the kidney interstitium and thyroid, and senile atrophy of the testis. The authors note these effects appear to reflect accelerated changes commonly associated with aging in hamsters.

In the hydrazine exposed rats, effects were observed in the respiratory tract of exposed animals. Specifically, squamous metaplasia of the larynx, trachea, and nasal epithelium (males only) was observed in the highest dose group (5.0 ppm hydrazine). Inflammation was also observed in the larynx and trachea of rats exposed to 5.0 ppm hydrazine. Increased incidence of focal cellular change of the liver was observed in female mice at 1.0 and 5.0 ppm hydrazine. Other effects with incidence found to be increased only in the high dose group include hyperplastic lymph nodes in females, endometriosis, and inflammation of the uterine tube.

The toxic effects from inhalation of hydrazine over a six month period from both intermittent and continuous exposure scenarios were examined (Haun and Kinkead, 1973). Groups of 8 male beagle dogs, 4 female rhesus monkeys, 50 male Sprague-Dawley rats, and 40 female ICR rats per dose group were continuously exposed to 0.2 or 1.0 ppm hydrazine or intermittently (6 hours/day, 5 days/week) to 1.0 or 5.0 ppm hydrazine. A control group consisted of equal numbers of animals. The experimental design was such that each intermittent exposure group had a time-weighted-average matching continuous exposure group. Dose-related body weight reductions were observed in all treated groups as well as evidence of hepatic degeneration, fatty deposition in the liver, central nervous system depression and lethargy, eye irritation, and anemia.

Toxic effects from the exposure of rats, mice, and dogs to airborne hydrazine at levels of 0, 4.6, or 14 ppm intermittently for 6 months were reported (Comstock *et al.*, 1954). Observed adverse effects included anorexia, irregular breathing, vomiting, fatigue, and emphysema in dogs; pulmonary congestion and emphysema in rats and mice; and lung and liver damage in rats.

Lymphoid bronchial hyperplasia was observed in guinea pigs exposed to 2-6 ppm hydrazine for 5 days/week for 19-47 days (Weatherby and Yard, 1955).

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Vernot *et al.*, 1985
Study population	Hamster
Exposure method	Inhalation
Critical effects	Amyloidosis and hemosiderosis of the liver; thyroid amyloidosis
LOAEL	0.25 ppm
NOAEL	Not observed
Exposure continuity	6 hour/day, 5 days/week
Exposure duration	1 year
Average experimental exposure	0.045 ppm for LOAEL group (0.25 x 6/24 x 5/7)
Human equivalent concentration	0.045 ppm for LOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
Subchronic uncertainty factor	1
LOAEL uncertainty factor	10
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.0001 ppm (0.1 ppb, 0.0002 mg/m^3, 0.2 µg/m^3)

Vernot *et al.*(1985) present a thorough examination of chronic health effects from inhalation exposure to hydrazine. This study was chosen for the development of the chronic reference exposure level because (1) it was conducted with an adequate number of animals, (2) the critical/sensitive adverse effect (degenerative change in the liver in hamsters) showed a dose-response relationship, (3) the findings of this study support data found in studies by other groups.

This study shows a dose-related increase in the incidence of amyloidosis and hemosiderosis in hamsters intermittently exposed by inhalation to levels of hydrazine greater than 0.25 ppm. Other effects noted at 0.25 ppm included weight depression during exposure, mineralization of the kidney, and amyloidosis of the thyroid. Haun and Kinkead (1973) have also noted lesions of the liver in dogs, monkeys, and mice exposed to hydrazine for 6 months by inhalation. Comstock *et al.* (1954) observed liver damage in groups of rats exposed to hydrazine vapors. The single case report of hydrazine inhalation toxicity in humans showed necrosis and degeneration of the liver (Sotaniemi *et al.*, 1971).

The strengths of the inhalation REL include the availability of chronic inhalation exposure data from a well-conducted study with histopathological analysis. Major areas of uncertainty are the lack of adequate human exposure data, the lack of reproductive and developmental toxicity studies, and the lack of observation of a NOAEL.

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CHRONIC TOXICITY SUMMARY

ISOPHORONE

(1,1,3-trimethyl-3-cyclohexene-5-one; 3,5,5-trimethyl-2-cyclohexene-1-one; isoforon; isoacetophorone)

CAS Registry Number: 78-59-1

I. Chronic Toxicity Summary

Inhalation reference exposure level	**2,000 μg/m^3**
Critical effect(s)	Developmental effects (reduced crown-rump length of female rat fetuses)
Hazard index target(s)	Development; kidney; alimentary system

II. Chemical Property Summary (HSDB, 1995)

Description	Water-clear liquid with a peppermint-like odor
Molecular formula	$C_9H_{14}O$
Molecular weight	138.21
Boiling point	214°C
Vapor Pressure	0.44 mm Hg at 25°C
Solubility	Slightly soluble in water, 12,000 mg/L water at 25°C; miscible in organic solvents.
Conversion factor	5.65 μg/m^3 per ppb at 25°C

III. Major Uses and Sources

Isophorone is used extensively as a solvent in some printing inks, paints, lacquers, adhesives, vinyl resins, copolymers, coatings, finishes, and pesticides, in addition to being used as a chemical intermediate (HSDB, 1995). Since this compound has many different applications, release to the environment may originate from a wide variety of industrial sources including iron and steel manufacturers, manufacturers of photographic equipment and supplies, automobile tire plants, and printing operations. Coal-fired power plants may also emit isophorone to the air. Although it is mostly a man-made compound, isophorone has been found to occur naturally in cranberries (ATSDR, 1989). Due to its high water solubility and short half-life in the atmosphere ($t_{1/2}$ <5 hrs), the most probable route of exposure to isophorone for the general population is ingestion of contaminated drinking water. Individuals living near hazardous waste sites may also be exposed to isophorone dermally, but not by inhalation (ATSDR, 1989). Occupational exposure may occur by inhalation or dermal contact.

IV. Effects of Human Exposures

In occupational monitoring studies, the time-weighted average concentration in breathing zones and workplace air of a screening plant ranged from 8.3-23 ppm and from 3.5-14.5 ppm, respectively (Samimi, 1982). Up to 25.7 ppm was detected in air of a silk screening printing plant in Pittsburgh, PA (Kominsky, 1983). The concentration in breathing zone samples from a decal manufacturing plant in Ridgefield, NJ was 0.7-14 ppm (Lee and Frederick, 1982). It was suspected that the reported eye and nose irritation of workers at the silk screening plant and at the decal manufacturing plant were the result of acute and subacute exposure to isophorone vapors.

No information is available concerning long-term exposure or pharmacokinetics of isophorone in humans (ATSDR, 1989). However, workers exposed to 5-8 ppm (28-45 mg/m^3) of isophorone for one month complained of fatigue and malaise (NIOSH, 1978). When concentrations were reduced to 1-4 ppm, no adverse effects were reported. Acute exposure studies in humans (up to 400 ppm for 1 to 4 minutes) resulted in eye, nose and throat irritation, nausea, headache, and dizziness or faintness (Union Carbide, 1963). Fifteen minute inhalation exposure to 10 ppm isophorone produced only mild effects in human subjects while 25 ppm produced irritation to eyes, nose, and throat (Silverman *et al.*, 1946).

V. Effects of Animal Exposures

Few reports have been published regarding the pharmacokinetics of isophorone in experimental animals. Isophorone was widely distributed in the major organs of the rat following 4 hour inhalation exposure to 400 ppm (ATSDR, 1989). Oral gavage of 4000 mg/kg body wt to rats and a rabbit also resulted in wide distribution of the chemical. The highest blood levels of isophorone were reached by 30 min in rabbits following oral gavage and had decreased dramatically by 21 hours, indicating rapid absorption and elimination of the chemical. Preliminary results of a pharmacokinetic study indicate that rats treated orally with ^{14}C-isophorone excreted 93% of the radiolabel in the urine, expired air, and feces in 24 hours (ATSDR, 1989). The highest levels of ^{14}C-isophorone were found in the liver, kidney, preputial gland, testes, brain, and lungs. Several metabolites were identified in the urine of orally dosed rats and rabbits, including 3-carboxy-5,5-dimethyl-2-cyclohexene-1-one, 3,5,5-trimethylcyclohexanol, and some glucuronide conjugates (Dutertre-Catella *et al.*, 1978). A portion of the chemical was excreted unchanged in expired air.

In an early inhalation study, 10 Wistar rats/group and 10 guinea pigs/group, all of mixed sex, were exposed to 0, 25, 50, 100, 200 or 500 ppm isophorone 8 hr/day, 5 days/week for 6 weeks (Smyth *et al.*, 1942). Increased mortality and reduced body weights were observed at 100 ppm and up in both species. However, eye and nose irritation was noted only at the highest dose. Minor changes in blood chemistry (increased polymorphonuclear cells and decreased lymphocytes) and urinalysis (increased albumin) of guinea pigs were seen only at the highest dose. Histopathology of the livers revealed no convincing treatment-related effect. Dilation of Bowman's capsule and cloudy swelling of the convoluted tubular epithelium occurred in

kidneys of animals (assumed to be both species) at 50 ppm and up. However, two controls also had slight lesions of the tubular epithelium. It was reported that lungs were often congested but dose levels for corresponding lung lesions were not provided. Later investigations determined that the isophorone used in this study was contaminated with appreciable amounts of compounds more volatile than isophorone (Rowe and Wolf, 1963). Therefore, some of the adverse effects (i.e., the lung lesions) may have been due to the contaminants. The presence of highly volatile contaminants would also result in inaccurate concentrations of isophorone used in the study.

In a 90-day feeding study, 20 CFE albino rats/group/sex were given isophorone in their diet at concentrations of 0, 750, 1500 or 3000 ppm. Four beagle dogs/group/sex received isophorone in gelatin capsules at concentrations of 0, 35, 75 or 150 mg/kg body wt-day (AME, 1972a,b). High dose rats exhibited slightly reduced weight gain compared to controls (8-10%) for most of the study. Average weight gain among the exposure groups of beagle dogs remained essentially unchanged during the entire study. Urinalysis, hematology and clinical chemistry indices found no treatment-related effects in the animals at either the interim or final toxicological examinations. Gross pathology and a limited histopathological examination observed no treatment-related effects in either species. Data on isophorone purity and possible loss of isophorone from rat diet due to vaporization were not presented.

In the most comprehensive isophorone toxicity study to date, 50 F344/N rats/group/sex and 50 B6C3F1 mice/group/sex were administered 0, 250 or 500 mg isophorone/kg body wt 5 days/week by oral gavage (in corn oil) for 103 weeks (Bucher *et al.*, 1986; NTP, 1986). Clinical signs of toxicity were not seen during the length of the study. However, several deaths in male and female rats at the high dose occurred early in the study. A steep decline in survival rate of high dose male rats occurred after week 90. Male and female rats and female mice in the high dose group exhibited only a slight decrease in body weight (<10%) compared to controls. A 13-week range finding study for the 2-year study did not find compound-related lesions in the kidney (or any other organs) of rats and mice exposed up to 1000 mg/kg body wt-day. However, pathological examination of rats exposed to isophorone for 2 years revealed non-neoplastic lesions in the kidney. Increased mineralization of the collecting ducts in isophorone-exposed male, but not female, rats was observed. This lesion was characterized by basophilic aggregates of mineral most often found in the medullary collecting ducts and occurred coincidentally with lesions of chronic nephropathy. Nephropathy was observed in almost half the female controls and nearly all the male controls. Isophorone exposure appeared to increase both the severity of nephropathy in low dose male rats and the incidence of nephropathy in dosed female rats, but the effects were not pronounced. However, the isophorone potentiation of nephropathy in rats may be due to 'male rat-specific nephropathy' and not have any relevance to human exposure (Strasser *et al.* 1988). Other adverse effects in kidneys of isophorone-treated male rats include tubular cell hyperplasia (in a dose-related manner) and epithelial hyperplasia of the renal pelvis. In mice, an increased incidence of chronic focal inflammation was observed in the kidneys of males, but was not considered treatment-related. A dose-dependent increase in fatty metamorphosis occurred in the adrenal cortex of male rats, but the biological significance of this change is unknown. All isophorone-exposed male mice had an increased incidence of hepatocytomegaly and coagulative necrosis of the liver. However, treatment-related liver lesions were not observed

in female mice. Increased incidence of hyperkeratosis of the forestomach was observed in dosed male and high dose female mice, but was probably not a treatment-related effect.

Published studies on possible reproductive effects of isophorone are lacking. An unpublished inhalation study conducted by a commercial laboratory (Bio/dynamics, 1984b) studied possible teratogenicity due to isophorone in rats or mice at inhaled doses up to 115 ppm. Groups of 22 female rats and 22 female mice were exposed to 0, 25, 50 or 115 ppm isophorone (6 hr/day) on gestational days 6-15. Maternal toxicity in rats included dose-dependent alopecia and cervical/anogenital staining. Low body weights (7-8%) were occasionally observed in the 115 ppm group. In mice, maternal toxicity was confined to slightly decreased weight (7-8%) on one day in the 115 ppm group. No significant differences were found in uterine implantations, fetal toxicity, and external and internal malformations among the animals. However, a slight, but significant, growth retardation in the form of decreased crown-rump length was present among the high dose fetal rats. Also, a slight, but insignificant, increase in extra ribs and/or rudimentary ribs was seen in rat and mouse fetuses at the highest dose. In a pilot study for this developmental toxicity investigation (12 females/species), exencephaly was observed in 1 rat and 1 mouse undergoing late reabsorption and in 2 live rat fetuses from dams exposed to 150 ppm isophorone on gestational days 6-15 (Bio/dynamics, 1984a). Exencephaly was not observed at any dose level in the primary study.

Contrary to the findings of the above report, Dutertre-Catella (1976) did not find adverse reproductive or developmental effects in rats exposed to 500 ppm isophorone (6 hr/day, 5 days/week) for 3 months before mating. Females had been exposed throughout gestation as well. The pups were not examined for internal malformations so the study was incomplete for determination of developmental effects.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Bio/dynamics 1984a,b
Study population	22 female mice/group, 22 female rats/group
Exposure method	Discontinuous whole body inhalation exposure during gestation (0, 25, 50 or 115 ppm)
Critical effects	Developmental effects (reduced crown-rump length of female rat fetuses) and teratogenicity (exencephaly in fetal rats and mice)
LOAEL	115 ppm for reduced crown-rump length of female rat fetuses
NOAEL	50 ppm
Exposure continuity	6 hr/day during gestation
Exposure duration	Days 6-15 of gestation
Average experimental exposure	12.5 ppm (50 x 6/24)
Human equivalent concentration	12.5 ppm (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))

LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.4 ppm (400 ppb, 2 mg/m^3, 2,000 μg/m^3)

The inhalation study by Bio/dynamics (1984a,b) presents data that indicate exposure during gestation may be the most sensitive indicator of non-neoplastic toxicity by isophorone. Exposure of pregnant rats to 115 ppm isophorone during gestation resulted in significant growth retardation of female rat fetuses (reduced crown-rump length). Exposure to 50 ppm isophorone, the NOAEL, produced no developmental effects. The authors claim that removal of the two shortest female fetuses from the statistical analysis results in no significant difference for growth retardation; therefore, this adverse effect is not significant. However, this selective culling before the statistical analysis is not scientifically appropriate in this case. In addition, the authors did not perform some of the scheduled fetal examinations. Otherwise, the growth retardation might have had even greater statistical significance. The pilot study (Bio/dynamics, 1984a) observed exencephaly in a few mouse and rat fetuses at 150 ppm. Exencephaly was not considered significant by the authors because it was not present in any fetuses of the primary study (Bio/dynamics, 1984b). However, exencephaly is included as a critical effect in this summary because it is considered a serious teratogenic effect that was present at a dose only slightly higher than the LOAEL of the primary study (115 ppm). Alopecia of adult female rats was observed in many of the exposed animals. However, this effect may be considered more of an acute dermal irritation than a chronic effect. In addition, cervical and anogenital staining seen in many exposed rats is not considered an 'adverse' effect.

A strength of the database for isophorone is the consistency of the REL when compared to the study by Bucher *et al.* (1986). Developing a chronic REL based on the adverse effects due to lifetime exposure (Bucher *et al.*, 1986) results in about the same REL (0.2 ppm) as that produced due to adverse effects during gestation (Bio/dynamics, 1984a,b). Weaknesses of the database for isophorone include the lack of human exposure data and the lack of long-term inhalation studies. However, the lack of human data may be due to isophorone's rather low potency for causing chronic, non-neoplastic, adverse effects. Also, inhalation of isophorone is most likely a minor route of exposure for the general population. Due to the insufficient characterization of the kidney nephropathy in the NTP study (Bucher *et al*, 1986; NTP, 1986), a subchronic or chronic study in a non-rodent species would enhance the database for isophorone. The conduct and publication of another comprehensive study of possible reproductive and developmental effects of isophorone in experimental animals would also strengthen the database.

VII. References

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